FS2.22:V 55/949
Pennsylvania State Library
DOCUMENTS SECTION
STATE LIBRARY OF PENNSYLVANIA
3 0144 00543408 9

1949

a symposium

ON CURRENT PROGRESS IN THE STUDY OF VENEREAL DISEASES

SPONSORED JOINTLY BY THE SYPHILIS STUDY SECTION AND THE AMERICAN VENEREAL DISEASE ASSOCIATION

FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
DIVISION OF VENEREAL DISEASE

FS2.22

Digitized by the Internet Archive
in 2016 with funding from
This project is made possible by a grant from the Institute of Museum and Library Services as administered by the Pennsylvania Department of Education through the Office of Commonwealth Libraries

https://archive.org/details/symposiumoncurre00nati

A SYMPOSIUM ON

CURRENT PROGRESS IN THE STUDY OF VENEREAL DISEASES

Held Under the Auspices
of
The Syphilis Study Section
Division of Research Grants and Fellowships
National Institutes of Health,
United States Public Health Service

In Conjunction With
The Eleventh Annual Session
of the
American Venereal Disease Association

AUDITORIUM OF THE FEDERAL SECURITY BUILDING
Washington, D. C.
APRIL 7 - 8, 1949

Published by the Division of Venereal Disease,
United States Public Health Service

FEDERAL SECURITY AGENCY

OSCAR R. EWING, *Administrator*

PUBLIC HEALTH SERVICE

LEONARD A. SCHEELE, *Surgeon General*

Editor: THEODORE J. BAUER, *Medical Director*

Chief, Division of Venereal Disease

✠

UNITED STATES GOVERNMENT PRINTING OFFICE, WASHINGTON : 1949

For sale by the Superintendent of Documents, U. S. Government Printing Office
Washington 25, D. C. - Price 75 cents

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

Division of Research Grants and Fellowships

SYPHILIS STUDY SECTION[1]

The Syphilis Study Section of the National Institutes of Health is a group of consultants organized for the purpose of promoting and developing research investigations in the field of venereal diseases. The membership of this Study Section is listed below. For additional information relative to Syphilis Study Section activities address Francis L. Schmehl, Executive Secretary, Syphilis Study Section, National Institutes of Health, Bethesda 14, Md.

Dr. J. E. Moore, Chairman, Johns Hopkins University.
Dr. Theodore J. Bauer, United States Public Health Service.
Comdr. William J. Dougherty, United States Navy.
Maj. C. M. Eberhart, United States Army.
Lt. Col. George B. Green, United States Air Force.
Dr. Bascom Johnson, Jr., Veterans Administration.
Dr. John F. Mahoney, United States Public Health Service.
Dr. Malcolm H. Merrill, California State Department of Public Health.
Dr. Hugo Muench, Harvard University.
Dr. Donald M. Pillsbury, University of Pennsylvania.
Dr. Harry C. Solomon, Boston Psychopathic Hospital.
Dr. Thomas B. Turner, Johns Hopkins University.

Subcommittee on
Biologic False Positive Serologic Tests

Dr. Hans Neurath, Chairman, Duke University.
Mr. John F. Kent, Duke University.
Dr Charles R. Rein, New York University.
Dr. John F. Mahoney, United States Public Health Service.

---

[1] The Syphilis Study Section is one of 23 groups of special consultants organized to aid the Division of Research Grants and Fellowships of the National Institutes of Health to promote, develop and correlate research in specific medical fields. For further information relative to the Public Health Service program of research grants in the medical sciences see "New Horizons in Medical Research," *Science*, December 13, 1946, or write to Medical Director David E. Price, Chief, Division of Research Grants and Fellowships, National Institutes of Health, Bethesda 14, Md.

THE AMERICAN VENEREAL DISEASE ASSOCIATION

The American Neisserian Medical Society was organized in 1934 in order to promote the control of gonorrhea by stimulating research in the diagnosis, medical and social pathology, and treatment of gonorrhea and by the dissemination of authoritative information among the medical profession and the general public. In 1946 the scope of the aims and activities of the organization was enlarged to include all of the venereal diseases and its name was changed to The American Venereal Disease Association. The affairs of the Association are conducted by an Executive Committee composed of the officers and three additional members. Membership of the Executive Committee for the period June 1948 to April 1949 was as follows:

J. R. Heller, M.D., Washington, D.C., President.
Stafford L. Warren, M.D., Los Angeles, Calif., Vice President.
Wm. L. Fleming, M.D., Boston, Mass., Secretary.
Ivan E. Martin, Los Angeles, Calif., Treasurer.
Thomas B. Turner, M.D., Baltimore, Md.
Bertha Shafer, M.D., Chicago, Ill.
Wm. A. Hinton, M.D., Boston, Mass.

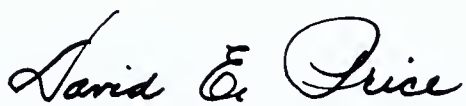
Additional information regarding the Association may be obtained from Wm. L. Fleming, M.D., Secretary, American Venereal Disease Association, 750 Harrison Ave., Boston 18, Mass.

Foreword

This symposium is the third to be held under the auspices of the Syphilis Study Section of the National Institutes of Health, and the first one to be sponsored conjointly with the American Venereal Disease Association. The support and assistance of the Association is gratefully acknowledged.

It is significant that these symposia bring together research workers from both the laboratory and the clinic, as well as public health specialists whose primary concern is venereal disease control. This leads not only to an effective exchange of ideas but also to the early adoption of practical advances in case finding, therapy and evaluation of methodology.

Many of the splendid presentations included in this forum were aided by research grants from the Public Health Service and it is gratifying to note the advances in this field which are the result of assistance by public funds. The unanswered questions which some of these studies so clearly define show that the problems of the venereal diseases were not solved with the advent of penicillin and that there must be a continuing effort both in research and in the application of control measures if these diseases are to be held in check.



DAVID E. PRICE, *Medical Director,*
Chief, Division of Research Grants and Fellowships,
National Institutes of Health.

Acknowledgment

Publication of the proceedings of this symposium has been made possible through the cooperation and editorial services of the Division of Venereal Disease, Public Health Service. The courtesies extended to me by the Division in these cooperative efforts are acknowledged with heartfelt thanks.

FRANCIS L. SCHMEHL,
Executive Secretary, Syphilis Study Section,
Division of Research Grants and Fellowships,
National Institutes of Health.

TABLE OF CONTENTS

SYPHILIS STUDY SECTION

Experimental Syphilis Page

Studies of the Life and Motility of *Treponema pallidum* in Fertile Hens' Eggs 1
Richard J. Rowe and Arthur C. Curtis

Summary of In Vitro Studies on the Cultivation of *Treponema pallidum* 5
Ruth A. Boak, Margarette L. Fawcett, and Charles M. Carpenter

Growth and Survival Factors for Cultivated and Pathogenic *Treponema pallidum* 12
H. G. Steinman and Harry Eagle

Immobilization of Virulent *Treponema pallida* by Antibody in Serum and Cerebrospinal Fluid of Syphilitic Patients 15
Robert A. Nelson, Jr., Judith A. Diesendruck, and Harold E. Zheutlin

The Susceptibility of Various Strains of Mice to Experimental Syphilis 18
Harold J. Magnuson, Barbara J. Rosenau, and J. W. Clark, Jr.

Penicillin Therapy

The Treatment of Early Syphilis with Three Injections of Penicillin and with One Injection of Penicillin 28
R. D. Wright, F. P. Nicholson, J. F. Mahoney, and R. C. Arnold

Treatment of the Syphilitic Pregnant Woman With Penicillin in Absorption-Delaying Vehicles 34
Norman R. Ingraham, Jr., Elizabeth Kirk Rose, and Herman Beerman

Final Report from Central Statistical Unit on Comparative Failure Rates for Early Syphilis Treated with Penicillin 40
Margaret Merrell

Association of Course of Serologic Response and Clinical Outcome in Early Syphilis Treated with Penicillin 45
R. V. Rider, M. T. Hoekenga, and M. S. Buerk

Neurosyphilis

Five Years of Penicillin Effect Alone on Neurosyphilis, Including Some Comparisons with Prepenicillin Methods 50
John H. Stokes, Mortimer S. Falk, and George D. Gammon

Penicillin Treatment of Late Neurosyphilis—One to Five-Year Follow-Up with Special Reference to Clinical Failures 74
David Landau, Israel Kopp, Augustus S. Rose, and Harry C. Solomon

Neurosyphilis III. Evaluation After Three Years of Treatment with Penicillin Alone and with a Combination of Penicillin and Malaria 82
Arthur C. Curtis, William T. Kruse, and Dorothy H. Norton

Page
Penicillin Failures in Neurosyphilis 93
Bernhard Dattner
Pathological Observations in Penicillin-Treated Neurosyphilis 97
George D. Gammon, F. H. Lewey, H. Dillon, G. Schwarz, and John H. Stokes
Cerebral Blood Flow and Oxygen Consumption in Neurosyphilis 104
John L. Patterson, Jr., Albert Heyman, and Fenwick T. Nichols, Jr.

Optic Atrophy and Cardiovascular Syphilis

Early Diagnosis of Syphilitic Primary Optic Atrophy 109
Joseph V. Klauder and George P. Meyer
The Treatment of Decompensated Cardiovascular Syphilis with Penicillin 122
Mortimer S. Falk, Joseph Edeiken, William T. Ford, and John H. Stokes
Treatment of Cardiovascular Syphilis with Penicillin 126
Gerald Flaum and Evan W. Thomas

Aureomycin in the Treatment of Venereal Diseases

Aureomycin and Chloromycetin in the Therapy of Granuloma Inguinale 131
Robert B. Greenblatt, Robert B. Dienst, Virgene Wammock, Calvin Chen, and Robert M. West
Aureomycin: Its Oral Administration and Effect on *Treponema pallidum* in Man 135
Robert R. Kierland, Wallace E. Herrell, and Paul A. O'Leary
Studies on the Effect of Aureomycin on *Treponema pallidum* 138
Richter H. Wiggall, Harold E. C. Zheutlin, E. Randolph Trice, DuMont F. Elmendorf, Jr., and R. C. V. Robinson

Read by Title

Report of Treatment with Fortified Penicillin of 248 Early Latent Syphilitic Mothers and Follow-Up 145
Belle Korman, Henry Eisenberg, Frederick Plotke, Hans Aron, and Jack Rodriquez
The Effect of Caronamide on Penicillin Blood Levels. A Comparative Study of 288 Males Given One-Day Treatment for Uncomplicated Gonorrheal Urethritis with Penicillin Alone, Caronamide Alone, and Penicillin Combined with Caronamide in Single and Multiple Oral Doses 148
Jack Rodriquez, Theodore J. Bauer, Frederick Plotke, W. W. Harris, and S. Weinstein
Report on Penicillin-Treated Patients with Optic Atrophy 161
J. V. Klauder and B. A. Gross
Preliminary Observations on the Treatment of Early Syphilis Utilizing Procaine Penicillin with Aluminum Monostearate 162
Arthur G. Schoch
The Validity of Withholding Treatment in the Presence of Dattner-Thomas Formula in the Spinal Fluid 162
S. F. Horne

Page

Abstract of The Jarisch-Herxheimer Reaction in Early Congenital Syphilis. A Study of 93 Patients Treated with Penicillin Alone.... 168
Harold A. Tucker and Osvaldo A. Pardo

Abstract of An Attempt to Produce Aortic Lesions of Syphilis in Experimental Animals..... 169
Fred A. Thompson and Harold J. Magnuson

Experimental Mouse Syphilis II. Minimal Infectious Number of *Treponema pallidum*..... 170
Paul D. Rosahn and Catharine L. Rowe

The Application of Studies of the Growth Requirements of *Neisseria gonorrhoeae* and of *Hemophilus ducreyi* to the Improvement of Methods for the Isolation of These Organisms from Clinical Material 175
J. H. Hill, E. E. Nell, and A. M. Mueller

Studies on Some Characteristics of the Pleuropneumonia Group of Organisms 183
M. H. Hatch

Aureomycin in the Treatment of Granuloma Inguinale..... 185
Raymond C. V. Robinson, DuMont F. Elmendorf, Jr., and Harold E. C. Zheutlin

AMERICAN VENEREAL DISEASE ASSOCIATION

Presidential Address

The New Threshold in Venereal Disease Control..... 193
J. R. Heller, Jr.

Immunity and Serology

The Duration of Acquired Immunity in Experimental Syphilis..... 196
Harold J. Magnuson, Barbara J. Rosenau, and J. W. Clark, Jr.

Immunological Relationships between Strains of *Treponema pallidum* 202
Thomas B. Turner and Mary C. Cumberland

The Role of Cardiolipin Antigens in the Serology of Syphilis..... 207
R. C. Arnold and J. F. Mahoney

Discussion of the Paper "The Role of Cardiolipin Antigens in the Serology of Syphilis" (by R. C. Arnold and J. F. Mahoney)..... 209
B. S. Kline

Gonorrhea

Delayed Administration of Oral Penicillin as Prophylaxis for Gonorrhea 212
V. W. H. Campbell, W. J. Dougherty, and C. E. Curtis

Revised Criteria of Cure in Gonorrhea..... 219
Adolph Jacoby and Theodore Rosenthal

Epidemiological Studies

Reports of the North Carolina Syphilis Studies. II. An Evaluation of Case-Finding Measures in Multiple Episodes of Infectious Syphilis 223
John J. Wright and Cecil G. Sheps

Page

Studies on Syphilis in the Eastern Health District of Baltimore City VIII. Reinfection and Relapse as a Component of the Discovery Rate 235
Fred C. Kluth and W. Thurber Fales

The Frequency of Discovery of Syphilis in Up-State New York between 1936 and 1943 241
William H. Haenszel and James H. Ladc

An Evaluation of Case-Finding Measures in the Control of Gonorrhea 251
John J. Wright and Cecil G. Sheps

Penicillin Studies

Penicillin in the Abortive Treatment of Syphilis 260
Frcdcrick Plotkc, Henry Eisenberg, Amelia H. Baker, and M. E. Laughlin

Abortive Treatment of Syphilis. Results Obtained in the Incubation, Primary, and Secondary Stages of Syphilis 267
Lee J. Alexander, Arthur G. Schoch, and Walter B. Mantooth

The Dynamics of Penicillin Action in Relation to its Use in the Treatment of Syphilis. A Recapitulation of the Experimental Data 272
Harry Eagle

Penicillin in Oil with Aluminum Monostearate: Its Effect on Prolonging Blood Concentrations of Penicillin and a Preliminary Report of its Use in the Treatment of Syphilis 276
S. R. Taggart, F. D. Hendricks, V. L. Chandler, Henry Welch, E. Q. King, D. M. Harley, and S. Olansky

Experiences with Single and Multiple Treatment Schedules of Early Syphilis with Procaine Penicillin in Oil and Aluminum Monostearate 283
Evan W. Thomas, Charles R. Rein, and Delmas K. Kitchen

Penicillin Therapy in Asymptomatic Neurosyphilis. A Comparison of the Effects of Amorphous Penicillin, Penicillin in Oil and Wax, and Crystalline Penicillin G on the Cerebrospinal Fluid 287
Fenwick T. Nichols, Jr. and Albert Heyman

Seropositivity in Patients Previously Treated for Syphilis. The Differentiation between Seroresistance and Treatment Failure 289
Ira Leo Schamberg

Read by Title

Advanced Banti's Syndrome Associated with Syphilis: Review and Report of Failure of Penicillin Therapy in Two Cases 294
George W. Hambrick, Jr. and Dudley C. Smith

Treatment of Gonorrhea with Oral Penicillin 300
Adolph Jacoby and Arthur H. Ollswang

Urethral Stricture—Sequela of Gonorrhea 302
R. Frank Jones

The Use of Cardiolipin-Lecithin in the Preparation of Indicator (Antigen) for the Hinton Test 302
William A. Hinton, Genevicve O. Stuart, and James F. Grant

False Positive Serologic Tests for Syphilis Due to Newcastle Virus Infection 308
Abraham Gelperin

Studies of the Life and Motility of *Treponema Pallidum* in Fertile Hens' Eggs[1]

Richard J. Rowe and Arthur C. Curtis

Fertile hens' eggs have been used as a possible medium for cultivation of *Treponema pallidum* (*1*, *2*, *3*, *4*, *5*). In 1938, Bessemans and De Meirsman (*1*) failed to culture *T. pallidum* by inoculating rabbit testicular tissue into fertile eggs. They found motile spirochetes after periods of from 24 to 48 hours but these were not infectious for rabbits. In 1939, Sterzi and Staudacher (*2*) placed fragments of darkfield positive rabbit testicular tissue on the chorioallantoic membranes of hens' eggs and found spirochetes near the site of implantation 24 hours later. These spirochetes were infectious for rabbits 2 hours after implantation but not later. In 1941, Callaway (*3*) found motile spirochetes at the end of 27 hours which were infectious when inoculated into the testicles of rabbits. Wile and Snow (*4*) reported experiments in which rabbits could be infected with material from eggs 8 days after these eggs had been inoculated with a darkfield positive rabbit testicular emulsion, and in 1943 Wile and Johnson (*5*) confirmed these findings. In neither of these last two instances were spirochetes found, and the authors suggested that infectivity might be attributed to the presence of an ultramicroscopic phase in the life cycle of *Spirocheta pallida.*

In 1906, Ehrlich (*6*) demonstrated that tumors of one species may survive for a period of 8 to 10 days when transplanted to closely related species, and in 1911 and 1912 Murphy (*7*, *8*) found that various tissues when transplanted to the chorioallantoic membrane would grow there. Since that time there have been a number of reports of growth of various types of tissue on these membranes. Goodpasture et al. (*9*) reported in 1938 that human skin grafted upon the chorioallantoic membrane was susceptible to certain viral infections.

The finding of spirochetes and the presence of infectivity in these eggs have not been parallel. Consequently, it has been suggested that an ultramicroscopic phase may be present in the life cycle of *T. pallidum* (*4*, *5*). We, therefore, attempted to graft *T. pallidum* infected tissue onto the chorioallantoic membranes of hens' eggs, and to determine whether in these preparations infectivity could be correlated with the presence of spirochetes.

[1] Studies and contributions from the Department of Dermatology and Syphilology, University of Michigan Medical School, Service of Dr. Arthur C. Curtis. This work was made possible by U.S. Public Health Service Research Grant No. 849.

Method

Fertile hens' eggs were incubated at temperatures between 37° and 38° C. for periods of 6 to 11 days prior to inoculation. These eggs were turned each day. The eggs were candled, cleaned with alcohol, and a rectangular area and a small triangular area in the side of the rectangle cut in the eggshell as described by Beveridge and Burnet (*11*). After the chorioallantoic membrane had been dropped, the shell and shell membrane of the rectangular area were removed, and the eggs were ready for tissue implantation.

Infected testicles were removed at 29 to 89 days after inoculation with a darkfield positive source of the Nichols strain of *T. pallidum*. This tissue was cut into pieces about 1 cm. square by 1 mm. in thickness. A piece of sterile cork, as described by Goodpasture and Anderson (*12*), and a sharp scalpel were used for this purpose. The pieces of tissue could be picked up with a forceps and placed on the membranes. Factors concerned in successful growth are discussed by Goodpasture, Douglas, and Anderson (*9*). Darkfields were done on testicular material before implantation, and on the grafts of each egg at the end of the period of observation. Chorioallantoic membranes, in eggs in which darkfield positive tissue was present at the end of the period, were examined in three different experiments.

Results

Infected tissue was placed on the chorioallantoic membranes in 11 different instances. Nine to fourteen eggs were used each time. In one experiment tissue was allowed to remain on the membranes for a period of 14 days at 35° C. At the end of that time darkfields were prepared and 100 fields examined from each of 8 eggs. Ten nonmotile spirochetes were found in 1 egg and 5 in another. No spirochetes were found in the remaining 6. The tissue from these 8 eggs was pooled and inoculated intratesticularly into a rabbit. At the end of 121 days there was no palpable nodule present in the testicle. At the end of 125 days both standard and quantitative Kahn serologic tests were negative.

Of the remaining 10 experiments, spirochetes were found in 8 at the end of 7 days. In 6 experiments the eggs were incubated at 35° C., in 1 experiment at 31° C., 1 at 32° C., and 2 at 33° C. At temperatures of 31° and 32° C., the eggs were dead at the end of 7 days, and spirochetes were neither more numerous nor in better condition at these temperatures than at higher temperatures. In the two experiments in which eggs were incubated at 33° C., active spirochetes with morphology and motion typical of

T. pallidum were present. Darkfield preparations were made from each egg by cutting a small slit in the tissue graft and rubbing it on a previously flamed slide. One hundred fields were examined in each preparation. Six motile spirochetes were seen in one preparation, 3 in the second, 2 in the third and fourth, and 1 in the fifth preparation. Nonmotile spirochetes were seen in other preparations. The tissue from each of the last 2 experiments was pooled separately and inoculated into the testicles of two adult rabbits. One rabbit developed a darkfield positive syphiloma in 23 days and the other in 32 days.

Treponema pallida were not found in darkfield preparations from chorioallantoic membranes around darkfield positive tissue. In two different experiments in which this tissue was inoculated into rabbits both developed darkfield positive syphilomas, one in 44 days and one in 39 days after inoculation. Chorioallantoic membrane was not examined in the former of these two experiments.

Of a total of nine rabbits inoculated, one died and six developed darkfield positive syphilomas. The spirochetes from these syphilomas had motion and morphology typical of *T. pallidum*. In each case there was a rise in the quantitative Kahn titer of the serum of from 20 to 320 Kahn units. During the course of these experiments the same strain of spirochetes was passed from rabbits to eggs and back to rabbits three times, with development of a darkfield positive syphiloma in the rabbit in each instance. Two of the above nine rabbits had not developed infection within a period of 4 months. At the end of this time the standard and quantitative Kahn on one rabbit's serum were negative; quantitative Kahn on the other's serum had changed from negative to 20 Kahn units. However, the second rabbit was inoculated with a virulent source of *T. pallidum* and developed a darkfield positive syphiloma within 29 days.

Comment

Sterzi and Staudacher (*2*) were able to find active spirochetes at 24 hours in darkfield preparations from the chorioallantoic membrane surrounding fragments of infected testicular tissue. They were unable to find either spirochetes or infectivity after 48 hours. Use of incubation temperatures of up to 38° C. may have been a factor in their failure. Although we did not find spirochetes in darkfield preparations from the chorioallantoic membrane, after periods of 7 and 14 days, we made no great effort to find them in this location because of the work involved in examining 800 to 1,000 fields in different tissue preparations. The longer

T. pallida stand at room temperature, the less virulent they become (*15*). This limits the available time for darkfield work.

Since spirochetes can be demonstrated in small pieces of tissue grafted onto the chorioallantoic membrane, and in saline suspensions at room temperature (*13*), they are also probably present in eggs into which an emulsion of testicular tissue has been inoculated. Magnuson (*15*) demonstrated that one or two spirochetes were regularly infectious when inoculated into a rabbit intratesticularly. However, demonstration of one or two spirochetes in an inoculum, by darkfield technic, may be a very difficult undertaking requiring examination of thousands of fields (*16*).

It has been known for many years that *T. pallida* would remain motile in a saline suspension of infected rabbit testicular tissue, at room temperature, for periods of up to 58 days (*13*). We do not feel that we have demonstrated growth of *T. pallidum* in fertile hens' eggs. The presence of spirochetes in tissue under these conditions is probably the same phenomenon observed previously in excised tissues (*13, 14*). However, these spirochetes were quite consistently infectious. Use of younger spirochetes, use of human tissue, and incubation of the eggs at 33° C. may give better results.

The spirochetes seen in these experiments were not similar to those described by Steinhaus and Hughes (*17*) as possibly occurring naturally in hens' eggs.

Summary

Typical actively motile, pathogenic *T. pallida* have been found in infected testicular tissue 7 days after this tissue was grafted onto the chorioallantoic membrane of fertile hens' eggs. Nonmotile spirochetes were found in similar tissue 14 days after it had been grafted onto the chorioallantoic membrane. Since spirochetes are present under these conditions they are also probably responsible for the infectiousness of eggs into which saline emulsions of infected testicular tissue had been inoculated.

Acknowledgment

We wish to express our appreciation to Dr. Thomas Francis, Jr., for his advice and material assistance in this work.

References

1. Bessemans, A.; De Meirsman, E.: Tentatives de culture de *Treponema pallidum* sur la membrane chorio-allantoidienne de L'Embryon de poulet vivant. Compt. rend. soc. de biologie, 127: 847, 1938.

2. STERZI, G.; STAUDACHER, V.: Tentativi di coltura della Spirochaeta di Schaudinn sulla membrana corionallantoidea di embrione di pollo vivente. Gior. ital di dermat. e sif., 80: 777, 1939.
3. CALLAWAY, J. L.; SHARP, J.: Cultivation of Spirochaeta pallida on the chorio-allantoic membrane of the developing hen egg. J. Lab. & Clin. Med., 27: 232, Nov. 1941.
4. WILE, U. J.; SNOW, J. S.: The chick embryo as a culture medium for *Spirocheta pallida*. J. Invest. Dermat., 4: 103, Apr. 1941.
5. WILE, U. J.; JOHNSON, S. A. M.: Further study of the chick embryo as a culture medium for the Spirochaeta pallida. Am. J. Syph. Gonor. & Ven. Dis., 28: 187, Mar. 1944.
6. EHRLICH, P.: Experimentelle carcinomstudien an Mausen Arb, a. d. k. Inst. f. exper. therapie, Frankfurt. No. 1, p. 77, 1906.
7. ROUS, P.; MURPHY, J. B.: Tumor implantations in the developing embryo. J.A.M.A., 56: 741, Mar. 11, 1911.
8. MURPHY, J. B.: Transplantability of malignant tumors to the embryos of a foreign species. J. A. M. A., 59: 874, Sept. 14, 1912.
9. GOODPASTURE, E. W.; DOUGLAS, B.; ANDERSON, K.: A study of human skin grafted upon the chorio-allantois of chick embryos. J. Exper. Med., 68: 891, 1938.
10. GOODPASTURE, E. W.; BUDDINGH, G. J.: The preparation of antismallpox vaccine by culture of the virus in the chorio-allantoic membrane of chick embryos and its use in human immunization. Am. J. Hyg., 21; 319, 1935.
11. BEVERIDGE, W. I. B.; BURNET, F. M.: The cultivation of viruses and rickettsiae in the chick embryo. Medical Research Council Special Report Series, No. 256: 14, London 1946.
12. GOODPASTURE, E. W.; ANDERSON, K.: Virus infection of human fetal membranes grafted on the chorio-allantois of chick embryos. Am. J. Path., 18: 563, 1942.
13. LACY, G. R.; HAYTHORN, S. R.: Viability of Spirochaeta pallida in excised tissue and autopsy material. Am. J. Syph., Gonor. & Ven. Dis., 5: 401, 1921.
14. SHAFFER, L. W.: Cultural methods for increasing the number of *Spirochaetae pallidae* in fresh syphilitic tissue. Arch. Path., 2: 50, 1926.
15. MAGNUSON, H. J.; EAGLE, H.; FLEISCHMAN, R.: The minimal infectious inoculum of Spirochaeta pallida and a consideration of its rate of multiplication in vivo. Am. J. Syph., Gonor. & Ven. Dis., 32: 1, Jan. 1948.
16. GUEFT, B.; ROSAHN, P. D.: Experimental mouse syphilis, a critical review of the literature. Am. J. Syph., Gonor. & Ven. Dis., 32: 59, Jan. 1948.
17. STEINHAUS, E. A.; HUGHES, L. E.: Isolation of an unidentified spirochete from hens' eggs after inoculation with liver tissue from hens. Pub. Health Rep. 62: 309, Feb. 28, 1947.

Summary of In Vitro Studies on the Cultivation of *Treponema Pallidum*[1]

Ruth A. Boak, Margarette L. Fawcett, and Charles M. Carpenter

The isolation of *Treponema pallidum* in vitro has intrigued the microbiologist ever since Schaudinn and Hoffman (*1*) established beyond doubt that a spirochete was the cause of syphilis. The

[1] From the Department of Infectious Diseases, School of Medicine, University of California, Los Angeles, Calif., and the Department of Investigative Medicine, Birmingham VA Hospital, Van Nuys, Calif. This investigation was supported by a research grant from the Division of Research Grants and Fellowships, National Institutes of Health, U.S. Public Health Service.

successful cultivation of the organism in vitro has been reported by many investigators. In 1929, Kast and Kolmer (*2*) reviewed the literature and noted that 30 investigators had isolated either pure or impure cultures of the spirochete from infected human or rabbit tissues. Virulent cultures of *T. pallidum*, however, could not be obtained by them from any of the bacteriologists alleged to have grown the organism. During the past 20 years, numerous attempts have likewise been made to obtain cultures of the virulent organism employing the newer technics such as tissue cultures and the use of embryonated eggs (*3, 4, 5, 6*). Wile and Snow (*5*) were able to produce syphilis in 2 rabbits by the intratesticular inoculation of tissues from eggs incubated for 8 days. A recent study by Nelson (*7*) has contributed excellent information on the biologic factors essential to the survival of *T. pallidum* in vitro.

Inoculum from human sources is notably unsatisfactory because of concomitant bacteria in the majority of syphilitic lesions. On the other hand, the syphilomata of experimental syphilis in rabbits can be obtained bacteria-free and constitute suitable specimens for studies on cultivation. Throughout the years of research on experimental syphilis in our laboratories, numerous attempts have been made to isolate *T. pallidum*.

The viability of the spirochete of syphilis was maintained on embryonated hens' eggs for 3 days and, more recently, motility was observed for 12 days in embryonated duck eggs which were employed because of the longer period of time required for them to hatch. The failure to grow the organism in eggs persuaded us to turn again to the use of lifeless media.

The present report comprises two somewhat different but related phases of the study: (1) attempts to isolate virulent strains of *T. pallidum* in vitro, and (2) to determine the effect of various nutritional factors in a basal medium on the viability of *T. pallidum*.

Materials and Methods

Inoculum

Indurated, testicular syphilomata, produced in rabbits from 27 to 39 days after inoculation, were employed. The testes were removed aseptically and small sections of the syphiloma, approximately a 2 mm. cube (20 mg.), were cut and transplanted directly into the medium. To date, cultures have been made from syphilomata in 21 rabbits. These include 6 strains of spirochetes, Nichols (15 rabbits), Tho (2 rabbits), and Ami, Fan, Est, and Rei (1 rabbit each). The strains were established in rabbits for from 37 years to 6 months (table 1).

Table 1.—*Observations in vitro of* Treponema pallidum *obtained from rabbits with experimental syphilis* [1]

Strain	Date of isolation of strain	Age of lesion in rabbit	Motile spirochetes observed			
			Original culture	First subculture	Second subculture	Third subculture
		Days	*Days*	*Days*	*Days*	*Days*
Nichols	1912	30	84	87	23	11
Ami	1939	29	34			
Fan	1946	34	97			
Tho	1948	27	66	25		
Est	1948	39	39			
Rei	1948	27	66	25		

[1] Observations to 21 March 1949.

Medium

The basal medium was Brewer's modified thioglycolate medium. Ten-percent serum inactivated 1 hour at 60° C. from one of the following species of animals was added: chicken, duck, goose, beef, and hog. The motility of *T. pallidum* was determined to persist longer in the above-named serums than in serum from the goat, guinea pig, rabbit, rat, horse, and sheep, in ascitic fluid or in a 30-percent bovine albumin (Armour). Such tests were carried out in a medium containing equal parts of brain-heart infusion broth (Difco) and one of the agents (table 2).

Supplements of various types were added to the basal medium in which 10.0-percent inactivated beef serum was incorporated. Forty-two substances in a 0.1-percent concentration were tested

Table 2.—*Medium for cultivation of* Treponema pallidum

I. Basic medium—Thioglycolate medium, Brewer's modified	
	Gm. per liter
Peptone (B-B-L trypticase and phytone)	20
Dextrose	10
Sodium chloride	5
Dipotassium phosphate	2
Sodium thioglycolate	1
Methylene blue	.002
Agar	.5
II. Serum [1]—Chicken, duck, goose, beef, hog	An amount to give final concentration of 10.0 percent
III. Supplements	To give final concentration
	Percent
Amino acids	0.1
Fatty acids	0.005, 0.01
Growth factors	.1

[1] Inactivated 60° C. for 1 hour.

for their action on growth and motility (table 3). The effect of eight fatty acids; butyric, capric, caproic, caprylic, lactic, lauric, linoleic, and myristic, in final concentrations of 0.005 percent and 0.01 per cent was observed. Four other supplements; choline chloride, folic acid, glutathione, and pyridoxine in final concentrations of 0.1 percent were studied. One milliliter of the medium in test tubes 100 × 11 mm. was used and stoppered to prevent evaporation. The cultures were incubated at 30° C. ± 0.5° C. Subcultures were made by transferring 0.1 ml. of the original culture to tubes of uninoculated medium.

Table 3.—*Supplements in basal medium in concentration of 0.1 percent*

1. dl-a-Alanine	22. l-Hydrosyproline
2. b-Alanine	23. dl-Isoleucine
3. Glycine	24. dl-Leucine
4. a-Amino-n-Butyric	25. l-Leucine
5. l-Arginine	26. dl-Lysine
6. Arginine (free base)	27. l-Lysine
7. dl-Asparagine	28. dl-Methionine
8. l-Asparagine	29. dl-Norleucine
9. dl-Aspartic acid	30. dl-Norvaline
10. l-Aspartic acid	31. dl-Ornithine
11. Betaine	32. dl-Phenylalanine
12. Citrulline	33. l-Phenylalanine
13. Creatine	34. l-Proline
14. Creatinine	35. dl-Serine
15. l-Cysteine	36. l-Tau ine
16. l-Cystine	37. dl-Threonine
17. l-Glutamic acid	38. Tryptophane, acetyl
18. dl-Glutamic acid	39. l-Tryptophane
19. dl-Histidine	40. dl-Tryptophane
20. l-Histidine, NF VIII	41. l-Tyrosine
21. Histidine (free base)	42. dl-Valine

Estimation of Number and Motility of Spirochetes

The method of estimating spirochetes in a given medium was patterned after that described by Nelson (*7*). Darkfield examinations were made on approximately 0.01 ml. of the medium placed with a calibrated loop beneath a 22-mm.-square cover slip. Spirochetes were counted in 25 oil immersion fields and the total was multiplied by the factor 120,000 to determine the number of organisms per milliliter. Counts were made on controls at the time a particular observation was initiated, and either 24 or 48 hours thereafter except in the case of cultures which were examined at 10-day intervals when it was noted that the spirochete had remained motile for several weeks.

Tests for virulence were made by intratesticular injection of normal, male rabbits with negative serologic tests for syphilis.

Results

Motile spirochetes morphologically characteristic of *T. pallidum* were observed for from 34 to 97 days in original cultures from syphilomata in 21 rabbits produced by six different strains of the organism.[2] The observations were repeated 15 times with the Nichols strain which was transmitted to rabbits in 1912. Similar cultures of spirochetes were obtained once each from strains identified as Ami, Fan, Est, and Rei, which were more recently adapted to rabbits. In the case of strain Tho, cultures were made from each of 2 rabbits (table 1). Motile spirochetes were seen in an original culture (Nichols strain) for 84 days, in a first subculture for 87 days, in a second subculture for 23 days, and in a third subculture for 11 days.

The number of motile spirochetes in the medium 24 hours after inoculation varied from 2 to 16 per 25 oil-immersion fields with an average of 10 per field equivalent to 1,200,000 spirochetes per milliliter. In many first and second subcultures, after 10 days' incubation in the basal medium containing either 10-percent inactivated goose or beef serum, from 10 to 25 spirochetes were observed in 25 oil-immersion fields, a number equivalent to or greater than that noted in the original culture. As a result of dilution they should contain only $\frac{1}{10}$ or $\frac{1}{100}$ as many spirochetes.

Among the 42 substances tested, betaine, citrulline, creatinine, and dl-ornithine were superior to the remaining 38. In one series employing the Nichols strain, an average of only one motile spirochete per 25 oil-immersion fields was observed for the 38 supplements in cultures examined on the tenth, twenty-fourth, and thirty-fourth days after inoculation. Counts from the medium with betaine made on similar days were 9, 3, and 4; for citrulline, 13, 14, and 10; for creatinine, 6, 12, and 8; and for dl-ornithine, 9, 3, and 4. In the control cultures in basal medium with 10-percent beef serum only, the number of motile spirochetes observed on the same 3 days was 1, 3, and 2 (table 4). Similar results were obtained with the Est strain, but the highest counts in this instance were noted in the medium containing either citrulline or dl-ornithine. Thus, the above four agents, on the basis of motile spirochetes counted, were from 5 to 10 times more effective than any of the other compounds tested. They appeared to either stimulate growth and/or preserve the organism so that motility was not lost.

Neither the addition of the fatty acids, butyric, capric, caproic, caprylic, lactic, lauric, linoleic, and myristic, in concentrations of

[2] Observations are still in progress.

Table 4.—*Results of supplementing basal medium with 10.0-percent inactivated beef serum and with other agents* [1] *on total motile spirochetes (Nichols strain) in 25 oil immersion fields*

Supplements	Age of culture (days)		
	10	24	34
Betaine	9	3	4
Citrulline	13	14	10
Creatinine	6	12	8
dl-Ornithine	9	3	4
Average, 38 other substances	1	1	1
Control—Basal medium with 10.0 percent inactivated beef serum	1	3	2

[1] Final concentration in medium, 0.1 percent.

0.005 and 0.01 percent, nor the growth factors, choline chloride, folic acid, glutathione, and pyridoxine, in concentrations of 0.1-percent increased the number of motile spirochetes when added to the basal medium with 10-percent inactivated beef serum.

Virulence tests were carried out only on the first subcultures of the Nichols, Rei, and Tho strains by the intratesticular inoculation of rabbits. Three rabbits injected with 19-, 34-, and 97-day-old cultures from the Nichols strain and observed for 72, 56, and 46 days, respectively, have, as yet, shown no clinical or serologic evidence of experimental syphilis. Rabbits inoculated with the cultures from the Rei and Tho strains have been observed for only 10 days.

Discussion

A report of motile spirochetes in cultures from syphilitic lesions constitutes passive interest for the bacteriologist and the syphilologist, but for the particular investigator they are of great concern. Are they, or are they not, *T. pallidum?* Without tests for their virulence in rabbits and no immunologic evidence, a valid statement of their significance cannot be made. On the other hand, the presence of motile spirochetes in cultures morphologically like *T. pallidum*, from typical syphilomata in rabbits produced by six different strains of the organism, suggested that they were *T. pallidum.* Cultures from the testes of normal rabbits showed no spirochetes and clinical evidence of infection with *T. cuniculi* was never detected.

Difficulty was encountered in determining the number of spirochetes per milliliter in the cultures and, specifically, whether growth took place or viability only was maintained. The inoculum consisting of one small 2-mm. cube cut from a syphiloma was in general uniform, but the number of spirochetes introduced into

each tube varied somewhat. In addition, a small amount of agar, 0.5 percent, in the basal medium interfered with making accurate counts. Repeated counts on series of cultures, however, showed from twenty- to fifty-fold increase over the number of spirochetes transferred from the original culture to the second and third subcultures. The counts were always made by two observers, who checked each other's observations with fairly close agreement. One cannot discount possible errors, however, resulting from sampling.

Although motility typical of *T. pallidum* was observed in the cultures, a change in motility often occurred. The lateral "whipping" motion disappeared in many of the cells, but rotation on the long axis and the translational movement was retained in most cultures. Nonmotile organisms in varying percentages were always present. Our observations made on the effects of the amino acids and their derivatives did not coincide with those of Eagle and Steinman (*8*), who observed that arginine in their medium stimulated the growth of the greatest number of the Reiter treponemes. It is significant, however, that best results were obtained with the two amino acids, citrulline and dl-ornithine, compounds closely related to arginine.

Although no evidence was obtained that the spirochetes in cultures resembling *T. pallidum* were virulent, only inadequate and incomplete work has as yet been carried out.

Summary

1. Motile spirochetes morphologically characteristic of *T. pallidum* were observed in cultures from 21 testicular syphilomata in rabbits produced by six different strains of the organism. Brewer's modified thioglycolate medium with either 10-percent inactivated goose or beef serum was employed. They were present in original cultures for from 34 to 97 days. In one series of first, second, and third subcultures (Nichols strain) motile spirochetes were seen for 87, 23, and 11 days, respectively.

2. Of 42 supplements added to the basal medium in a 0.1-percent concentration, betaine, citrulline, creatinine, and dl-ornithine, were most beneficial in maintaining the greatest percentage of motile spirochetes.

3. Neither the addition of eight fatty acids, butyric, capric, caproic, caprylic, lactic, lauric, linoleic, and myristic, in concentrations of 0.005 and 0.01 percent, nor the growth factors, choline chloride, folic acid, glutathione, and pyridoxine, in concentrations of 0.1 percent, increased the number of motile spirochetes when

added to the basal medium with 10-percent inactivated beef serum.

4. Tests for virulence were carried out on the first subcultures of three strains only, Nichols, Rei, and Tho, by the intratesticular inoculation of rabbits. These observations are incomplete.

References

1. Schaudinn, F.; Hoffmann, E.: Vorlaufiger Bericht uber das Vorkommen von Spirochaeten in syphilitischen Krankheitsprodukten und bei papillomen. Arb. k. Gsndhtsamte, 22: 527, 1905.
2. Kast, C. C.; Kolmer, J. A.: Concerning the cultivation of *Spirocheta pallida*. Am. J. Syph., Gonor., & Ven. Dis., 13: 419, 1929.
3. Kast, C. C.; Kolmer, J. A.: On the cultivation of *Spirocheta pallida* in living tissue media. Am. J. Syph., Gonor., & Ven. Dis., 17: 529, 1933.
4. Sterzi, G.; Standacher, V.: Tentativi di coltura della Spirocheta di schaudinn sulla membrana corionallantoidea de embrione de pillo vivente. Gior. ital. di dermat. e sif., 80: 777, 1939.
5. Wile, U. J.; Snow, J. S.: Chick embryo as a culture medium for *Spirochaeta pallida*. J. Invest. Dermat., 4: 103, 1941.
6. Callaway, J. L.; Sharp, J.: Cultivation of *Spirochaeta pallida* on the chorioallantoic membrane of the developing hen egg. J. Lab. & Clin. Med., 27: 232, 1941.
7. Nelson, R. A.: Factors affecting the survival of *Treponema pallidum* in vitro. Am. J. Hyg., 48: 120, 1948.
8. Eagle, H.; Steinman, H. G.: The nutritional requirements of Treponemata. J. Bact. 56: 163, 1948.

Growth and Survival Factors for Cultivated and Pathogenic *Treponema Pallidum*

H. G. Steinman and Harry Eagle

It had previously been shown in this laboratory (*1*) that the nonpathogenic Reiter strain of *Treponema pallidum* could be cultivated on a semisynthetic medium consisting of arginine, acetic acid, certain sulfur-containing substances, crystalline serum albumin, and a small amount of Brewers' thioglycolate medium, together with ascorbic acid and phosphate buffer. Of the several constituents of the thioglycolate medium, three components were considered as potentially capable of supplying nutritional factors: (1) trypticase, an enzymatic digest of casein; (2) yeast extract, a potent source of B vitamins; and (3) glucose. On examination of the separate components of the thioglycolate medium it was found that the enzymatically hydrolyzed casein was the critical constituent. Neither glucose alone nor yeast extract alone could support growth, but trypticase alone could.

Enzymatic digests of other proteins were observed to function similarly as a substitute for the whole thioglycolate medium. Using amigen, an enzymatic casein digest, as a substitute for trypticase, it was found that, as the amigen concentration fell below 1 part per 1,000 the growth response was reduced and became directly dependent upon the amigen concentration. At these subliminal concentrations of amigen both pantothenic acid and glutamine could be shown to have a growth-promoting activity and to substitute in part for the amigen deficiency. At higher concentrations of amigen (1 part per 1,000 and higher) added pantothenic acid and glutamine had no significant effect, the amigen presumably supplying these (or equivalent factors) as concomitant components.

The growth-promoting effects of these various factors are directly dependent upon their concentrations. The relatively low maximal growth response with glutamine and with pantothenic acid, reflects the fact that low concentrations of amigen must be used in order to detect the deficiency in these two factors, and other factors as yet undetermined are probably present in inadequate concentrations. In the case of acetic acid and arginine high concentrations are required for maximum growth. Slightly lower concentrations of glutamine are necessary for a good response. The cysteine curve shows a near-vitamin response, being effective at low concentrations, and the pantothenic acid curve shows a true vitamin response, being effective at very low concentrations.

The higher concentrations of the crude enzymatic digest apparently supply glutamine and pantothenic acid as, what might be called, impurities. These are factors which would not be present in the acid hydrolyzed protein digests used by Little and SubbaRow (*2*) and Whiteley and Frazier (*3*) in their studies with the Reiter treponeme. This difference between the two types of protein digests explains the fact that these authors found added vitamins to be essential to their medium, in contrast to our findings that a high-amigen-containing medium required no added vitamins.

Studies with the pathogenic *T. pallidum* to date have, of necessity, been confined to survival factors rather than growth factors, percentage of motile organisms being the measure of survival. The efficacy of carbon dioxide and of serum albumin as survival factors have been reported by Nelson and Steinman (*4*). It has since been shown by Nelson (*5*), and independently found by us, that sulfhydryl-containing compounds and also pyruvic acid exert a beneficial action on survival. In addition, serum ultrafiltrate has been found to prolong markedly survival time of *T. pallidum*, separated from tissue extractives by centrifugation. Even with

noncentrifuged organisms which, because of accompanying tissue extractives, survive for a longer time than do centrifuged spirochetes under parallel conditions, serum ultrafiltrate still exerted a beneficial if less pronounced action.

Although oxygen is known to be toxic to the pathogenic treponeme, the mechanism of this action is not clearly understood. The rapid cessation of motility under the impact of oxygen was only slightly delayed by the addition of ascorbic acid despite the fact that this latter system remained in the reduced state with respect to methylene blue. Added ascorbic acid had no toxic effect on a system containing reduced glutathione and, if anything, was protective against air exposure.

The question of whether oxygen exerts its effect directly or through hydrogen peroxide is being investigated. Although hydrogen peroxide formation is a mechanism which is known to account for the toxicity of air for many organisms (*6*), the probability is against hydrogen peroxide mediation in this system. The effect of oxygen itself is marked, indicating a rapid reaction with some oxidizable substrate, while hydrogen peroxide could probably arise only as a byproduct of oxygen oxidation.

In summary, then, it can be seen that while the studies with the Reiter spirochete have served as a model for the investigation of the more fastidious pathogenic treponeme, enough data are on hand to indicate that the metabolism of the two spirochetes follows different pathways. The two organisms have in common their requirement of a sulfhydryl-containing compound, serum albumin, and a strong reducing agent. The nonpathogenic organism requires in addition arginine, acetic acid, glutamine, pantothenic acid, and as yet unidentified components occurring in small amounts in enzymatic casein digests. The survival of the pathogen is promoted by the presence of carbon dioxide, pyruvic acid and serum ultrafiltrate. Studies are in progress as to the mechanism of action of the known factors and the determination of new growth and survival factors for both the nonpathogenic and pathogenic treponemes.

References

1. Eagle, H.; Steinman, H. G.: J. Bact. 56: 163, 1948.
2. Little, P. A.; SubbaRow, Y.: J. Immunol. 50: 213, 1945.
3. Whiteley, H. R.; Frazier, C. N.: Am. J. Syph., Gonor. & Ven. Dis., 32: 43, 1948.
4. Nelson, R. A.; Steinman, H. G.: Proc. Soc. Exper. Biol. & Med. 68: 588, 1948.
5. Nelson, R. A.: Am. J. Hyg. 48: 120, 1948.
6. Hewitt, L. F.: Oxidation-Reduction Potentials in Bacteriology and Biochemistry. London County Council, 1948.

Immobilization of Virulent *Treponema Pallida* by Antibody in Serum and Cerebrospinal Fluid of Syphilitic Patients[1]

Robert A. Nelson, Jr., Judith A. Diesendruck, and Harold E. Zheutlin

A method has recently been developed whereby antibody which immobilizes virulent *Treponema pallida* in vitro in conjunction with complement may be demonstrated in the serum of syphilitic animals and human beings. By absorption experiments the immobilizing antibody was shown to be separate from reagin, the antibody detected with the ordinary lipoidal antigens derived from normal tissue. Details of the treponemal immobilization test may be found in a paper by Nelson and Mayer in the *Journal of Experimental Medicine* (*1*).

It is the purpose of the present paper to summarize the results obtained in a survey of serums from normal individuals, from patients with diseases other than syphilis, from patients in various stages of syphilitic infection, and from a small group of patients with presumed "biological false positive" serologic reactions. Preliminary data on the kinetics of the immobilization phenomenon are also presented.

Table 1 shows the results of the survey of serums from human individuals. Serums were collected and stored under aseptic conditions, inactivated at 56° C. for 30 minutes just prior to use, and tested at a final dilution of 1:10 by mixing with tissue-free suspensions of treponemes in the presence of guinea pig complement.

Table 2 shows the results of a preliminary survey of cerebrospinal fluids from human individuals. Fluids were tested in a manner identical with that used for testing serums.

Since results of the survey of serums from normal and syphilitic individuals indicated that treponemal immobilizing antibodies occur with a high frequency in syphilitic patients, and was not detected either in normal individuals or in patients with diseases other than syphilis, it became of interest to examine patients whose serums contain a substance which reacts with one or more of the standard lipoidal antigens, despite the absence of syphilis. These include seven cases of atypical pneumonia, two of measles, one of infectious mononucleosis, and one of chicken pox. All of the serum specimens obtained from these patients were completely negative for immobilizing antibody despite the presence of a

[1] From the Department of Bacteriology of the Johns Hopkins University, School of Hygiene and Public Health.

Table 1.—*Survey of human serums for treponemal immobilizing antibody*

Classification	Number tested	Immobilization test		
		Positive	Doubtful	Negative
Normal	20	0	0	20
Other diseases	50	0	0	50
Primary syphilis [1]	20	10	3	7
Secondary syphilis [1]	20	20	0	0
Latent syphilis	20	20	0	0
Tertiary syphilis [2]	20	20	0	0
Congenital [2]	5	5	0	0

[1] Darkfield positive cases only.
[2] Symptomatic cases only.

Table 2.—*Survey of human cerebrospinal fluids for immobilizing antibody*

Classification	Number tested	Immobilization test		
		Positive	Doubtful	Negative
Nonsyphilitic	10	0	0	10
Latent syphilis	5	1	4	0
Asymptomatic C.N.S. syphilis	5	5	0	0
Symptomatic C.N.S. syphilis	5	5	0	0

positive test for reagin with one or more of the standard lipoidal antigens.

In addition, serums from eight private patients of Dr. J. E. Moore, who were diagnosed as presumed "biological false positive" reactors, were negative when tested for immobilizing antibody.

Therefore, it appears possible that a persistently negative treponemal immobilization test on an individual's serums may be of aid in excluding the diagnosis of syphilis. Further studies to confirm or reject this hypothesis are in progress.

The data obtained to the present time on the treponemal immobilizing antibody may be summarized as follows:

1. Absorption experiments have demonstrated that the treponemal immobilizing antibody is distinct from reagin.

2. Indirect evidence indicates that the immobilizing antibody is specifically directed against *T. pallidum*, since it was present in all of 65 cases of well-established syphilitic infection in humans, and could not be detected in 20 normal individuals, 50 patients with diseases other than syphilis, nor in 19 patients with presumed "biological false positive" reactions. Further, it exerts a specific in vitro effect, i.e., immobilizing and rendering the virulent treponeme noninfectious, and it exerts this effect *only* in the presence of complement.

3. Previous studies of individual serums from rabbits infected for periods up to 12 months demonstrated that relatively high serum levels of immobilizing antibody were present. In present studies on cases of latent and tertiary syphilis in human beings similar high levels were found. This persistent high level of immobilizing antibody was of striking contrast, in certain serums, to the low titer of reagin present. The general impression received up to the present time from observations on experimental syphilis in rabbits is that there is a marked divergence in the titers of reagin and immobilizing antibody with progress of the disease into the latent stage, i.e., the reagin titer diminishes while immobilizing titer remains elevated and more closely approximates the degree of immunity present, as measured by resistance to reinfection. It is possible that the same pattern holds for syphilis in man. This behavior of the immobilizing antibody as well as the fact that it renders virulent organisms noninfectious, indicates that this antibody may be closely associated with immunity in syphilis.

4. Four laboratory observations on the kinetics of the immobilization phenomenon are pertinent in discussing application of this test in further studies. First, the presence of small concentrations of tissue extract in the treponeme suspension does not significantly alter the rate of immobilization by antibody in the standard technic now used. No difference in the rate of immobilization of a given batch of treponemes was observed when the organisms were suspended in the usual manner in basal medium plus tissue extract as contrasted with washed treponemes resuspended in a medium of known chemical composition, which has been developed in our laboratory and which is capable of supporting survival of the organisms for at least 2 to 3 days (*2*). Second, the test procedure as now used was found to be reproducible within a threefold dilution of serum, when an individual pool of syphilitic rabbit serum was tested for 50-percent immobilizing capacity against five different batches of treponemes. Third, during the course of these studies in which about 200 individual serums have been tested, inconclusive results, i.e., immobilization of treponemes in both the complement-containing test mixture and in the complement-free control suspension, have occurred with eight serum specimens. Seven of these eight patients were receiving penicillin therapy at the time the serum was withdrawn, and it appears that this antibiotic in the serum was responsible for the nonspecific immobilization observed. In one patient, the factor responsible was not determinable. Fourth, since the immobilization phenomenon is a biological reaction which intimately depends on the

presence of complement, false negative results must be guarded against. At the termination of each experiment all mixtures of treponemes, serum, and complement which fail to show immobilization are tested for the presence of free complement by the addition of sensitized red blood cells.

5. More extensive clinical application of the immobilization test awaits cultivation of the pathogenic treponeme. Nevertheless, this technic or, more properly, the principles revealed by this technic, offer a convenient in vitro approach to the study of certain fundamental problems in the biology and immunology of syphilitic infection in animals and human beings. Some of these which are already in progress include: (1) a careful evaluation of the rate of development of this antibody in rabbits infected with syphilis and of the effect of treatment on serum antibody levels; (2) an attempt at defining the role of this antibody in immune processes at work in syphilis; (3) the use of the immobilization test to determine the immunologic relationship between various strains of *T. pallidum*, as well as the immunologic relationship between yaws and syphilis; (4) an attempt to study thoroughly the kinetics of the immobilization phenomenon on a quantitative basis so that accurate serum titers may be estimated; and (5) the information obtained in these various studies may be used in investigations of perplexing problems in clinical syphilis, such as the biologic false positive reactor.

References

1. Nelson, R. A.; Mayer, M. M.: Immobilization of *Treponema pallidum* in vitro by antibody produced in syphilitic infection. J. Exper. Med., 89: 369, April 1949.
2. Nelson, R. A.; Rice, F. A. H.: Further studies on factors affecting the survival of *Treponema pallidum* in vitro. (To be published).

The Susceptibility of Various Strains of Mice to Experimental Syphilis [1]

Harold J. Magnuson, Barbara J. Rosenau, and J. W. Clark, Jr.

Kolle and Schlossberger (*1*) were the first of many to demonstrate that the mouse can be infected asymptomatically with *Treponema pallidum*. In spite of the considerable work done since

[1] From the Syphilis Experimental Laboratory, U. S. Public Health Service, University of North Carolina, Chapel Hill, N. C. Aided in part by a Research Grant of the Research Grants Division, National Institutes of Health, U. S. Public Health Service.

1926, recently reviewed by Gueft and Rosahn (*2*), there are many variables in this infection which remain either uninvestigated or poorly understood. The inoculation of a few or single mice from various species has been described (*3*, *4*, *5*), but search of the literature reveals no systematic studies on the relative susceptibility of various strains of a single species of the mouse. Since Pierce, Dubos, and Middlebrook (*6*) demonstrated considerable differences in the susceptibility of various strains of mice to infection with *Mycobacterium tuberculosis*, it was felt that such an investigation of strain variation should be undertaken in experimental syphilis. The present report indicates that among nine strains of the same species of mice (*Mus musculus*) infected with the Nichols strain of *T. pallidum*, there was a wide variation in susceptibility to the infection as measured by the relative infectiousness of the mouse tissues on transfer to rabbits. In none of the nine strains tested did symptomatic infection develop.

Methods and Materials

Experiments were limited to male mice weighing between 15 and 20 gm. at the time of inoculation. The following were sources for the nine strains tested[2]: Carworth Farms, New City, N. Y., CF-1, CFW, CW, and Chocolate Brown strains; the National Institutes of Health, C_3H and C-57 black strains; The Jackson Memorial Laboratory, Bar Harbor, Maine, dba-line-1 strain. The strain designated in this paper as State Laboratory strain was obtained by the North Carolina State Board of Health Laboratory from the New York Division of Laboratories and Research at Albany, N. Y., some 9 years ago. It had been bred by the New York laboratory for 20 years and by the North Carolina State Farm for 8 years at the time these tests were performed.

In this laboratory, the mice were housed in groups of 5 to 10 in an air-conditioned room at a temperature of approximately 70° F. Purina dog chow and water were given ad libitum. The inoculum was an emulsion prepared from acute testicular syphiloma of rabbits inoculated 14 days before with 10^7 *T. pallidum* (Nichols strain) in each testis. The emulsions were prepared and suitably calibrated in the manner previously described (*7*) so as to contain 5×10^6 organisms per cubic centimeter. Each mouse received 0.2 cc. or 10^6 organisms intraperitoneally. The size of the experiment precluded simultaneous inoculation with the same emulsion, and the animals were inoculated in three

[2] The authors wish to acknowledge the kindness of the Carworth Farms; Dr. W. E. Heston, National Institutes of Health; The Roscoe B. Jackson Memorial Laboratory; and Dr. John H. Hamilton, State Laboratory of Hygiene, Raleigh, N. C., in making these strains available.

groups. Since the method of preparation of these emulsions has given remarkably uniform results in rabbits over the past 3 years (*8*), and since both high and low susceptibilities were encountered in the same inoculation groups, it is unlikely that variations in the inoculum could account for the observed differences among the strains.

Previous experiments (*9*) had indicated that with such an inoculum satisfactory infection of the CFW and CF-1 strains was produced within 4 weeks. Four weeks after inoculation the mice were killed by exsanguination from the heart, the tissues removed as indicated below, and separately ground in a mortar and pestle with 1 cc. of 50-percent normal rabbit serum. The entire cerebrum, spleen, contents of the popliteal fossae (lymph nodes), the gastrocnemius muscles, a lobe of the liver, and the blood from cardiac puncture were the tissues assayed. Care was taken to flame the instruments between tissue removals to prevent transfer of spirochetes from one tissue to another. After thorough grinding, one-fifth of each emulsion was inoculated intracutaneously into each of 5 sites on the backs of five different rabbits. From 12 to 24 sites were inoculated on each rabbit. Each mouse tissue was thus tested for infectivity at five different sites, all on different animals. Such a method served to minimize the susceptibility variations among the rabbits, and at the same time provided a crude quantitation of the infectiousness of the tissue.

The inoculated sites were examined weekly during a 3-month period. Lesions developing at any of the sites were considered positive only if *T. pallidum* could be found on darkfield examination. In a few instances, the transfer rabbits were retained for a 4-month observation period, but no additional lesions developed during the additional observation period.

Results

Shown in tables 1 and 2 are the results of these tissue transfers. The mouse strains are arranged from top to bottom in order of decreasing susceptibility, and the tissues are arranged in order of decreasing susceptibility from left to right. Table 1 is in detail to emphasize the tremendous variation among individual mice and tissues of these mice even within the same strain. Twenty mice of each strain were inoculated, but the present report is limited to 10 mice of each strain killed 4 weeks after inoculation. The remainder are being carried for 1 year after inoculation before killing and transfer. These will be the subject of a later report. Shown in the body of the table are the number

Table 1.—*The susceptibility of nine strains of mice to infection with the Nichols strain of* T. pallidum

[The strains of mice are arranged in order of descending susceptibility as measured by the infectiousness of their tissues on transfer to rabbits. Shown in the body of the table are the number of transfer sites which became positive for that particular mouse and tissue. Since five sites were inoculated from each tissue, this number represents the maximum for any one time.]

Strain	Mouse No.	Tissues and sites positive on transfer of mouse tissue to rabbits						Total tissues positive	Total sites positive
		Spleen	Liver	Brain	Blood	Lymph Node	Muscle		
CFW	1	1	1					2	2
	2	4		5				2	9
	3	5	4					2	9
	4	5	5	5		1	1	5	17
	5	4	2	3	4	1	1	6	15
	6	4	3	2	1	1	1	6	12
	7	2	3	3				3	8
	8	5	5	5	1			4	16
	9			1				1	1
	10	5	3	4	2			4	14
	+mice	9	8	8	4	3	3		
	−mice	1	2	2	6	7	7		
	+sites	35	26	28	9	3	3		
CF-1	1	2		2				2	4
	2	5	4	5	3			4	17
	3	5			1			2	6
	4	5	2		4			3	11
	7	5	1	3	1			4	10
	8			1				1	1
	9	1	1	2	1			4	5
	10	5	3	1				3	9
	+mice	7	5	6	5	0	0		
	−mice	8	3	2	3	8	8		
	+sites	28	11	14	10	0	0		
C_3H	1								
	2	1		2				2	3
	3			1				1	1
	4	2						1	2
	5	2		2	2			3	6
	6	1	1	3		1		4	6
	7	4	2	4			1	4	11
	8	1						1	1
	9	2	2	3				3	7
	10		1					1	1
	+mice	7	4	6	1	1	1		
	−mice	3	6	4	9	9	9		
	+sites	13	6	15	2	1	1		
CW	1	2	1				1	3	4
	2	3	1		1			3	5
	3					2		1	2
	4					3		1	3
	5	1		1				2	2
	6	4	3			4		3	11
	7			1	2			2	3
	8	1						1	1
	9	3	2			3		3	8
	10		3					1	3
	+mice	6	5	2	2	4	1		
	−mice	4	5	8	8	6	9		
	+sites	14	10	2	3	12	1		

Table 1.—*The susceptibility of nine strains of mice to infection with the Nichols strain of* T. pallidum—Continued

Strain	Mouse No.	Tissues and sites positive on transfer of mouse tissue to rabbits						Total tissues positive	Total sites positive
		Spleen	Liver	Brain	Blood	Lymph Node	Muscle		
C-57 black	1								
	2	3	2		1			3	6
	3	2						1	2
	4		1	3				2	4
	5	1	1					2	2
	6	2	1	5				3	8
	7	2	2	1				3	5
	8								
	9	1						1	1
	10	1						1	1
	+mice	7	5	3	1	0	0		
	−mice	3	5	7	9	10	10		
	+sites	12	7	9	1	0	0		
Chocolate	1		1		1			2	2
	2								
	3	1	2	2	1			4	6
	4		1			3		2	4
	5	1				4		2	6
	6	1						1	1
	7					1		1	1
	8		1					1	1
	9	1	1			5		3	7
	10								
	+mice	4	5	1	2	4	0		
	−mice	6	6	9	8	6	10		
	+sites	4	6	2	2	13	0		
dba-line 1	1								
	2	1	1					2	2
	3								
	4			1			1	2	2
	5			1		1		2	2
	6	1						1	1
	7								
	8	1	3	2		1		4	7
	9								
	10								
	+mice	3	2	3	0	2	1		
	−mice	7	8	7	10	8	9		
	+sites	3	4	4	0	2	1		
State Laboratory	1			1			1	2	2
	2			3	1			2	4
	3			3				1	3
	4								
	5								
	6								
	7								
	8	1	1	3				3	5
	9								
	10			3				1	
	+mice	1	1	5	1	0	1		
	−mice	9	9	5	9	10	9		
	+sites	1	1	13	1	0	1		

Table 1.—*The susceptibility of nine strains of mice to infection with the Nichols strain of* T. pallidum—Continued

Strain	Mouse No.	Tissues and sites positive on transfer of mouse tissue to rabbits						Total tissues positive	Total sites positive
		Spleen	Liver	Brain	Blood	Lymph Node	Muscle		
Brown Spot	1								
	2								
	3			1				1	1
	4			2				1	2
	5								
	6	2						1	2
	7								
	8	1						1	1
	9								
	10	1						1	1
	+mice	3	0	2	0	0	0		
	−mice	7	10	8	10	10	10		
	+sites	4	0	3	0	0	0		

of inoculated sites from that mouse tissue which became positive. Since five sites were inoculated from each mouse tissue, five represents the maximum infectiousness as here tested. No entry indicates that no lesions developed at any of the five sites. Details are eliminated in figure 1 in which the data of table 2 are consolidated in three-dimensional form with the vertical ordinate representing the percentage of tissues positive at one or more sites.

The extreme variation among strains and among mice of the same strain is at once apparent. It should be pointed out that such differences would have been missed had pools of the organs from a given mouse been inoculated. As Rosahn and his coworkers (*10*) have pointed out, such a pooling technic was the method employed by the majority of earlier workers. By such a pooling technic, in the present experiments 100 percent of the CFW, CF-1 and CW mice would have been positive (c.f. table 2), 90 percent of the C_3H, 80 percent of the C-57 black and Chocolate strains, and 50 percent of the dba-line-1, State Laboratory and Brown Spot strains.

Susceptibility might better be determined on the basis of the number of positive tissues within each strain tested. Such classification lists the mice in decreasing order of susceptibility as follows: CFW, CF-1, C_3H, CW, C-57 black, Chocolate, dba-line 1, State Laboratory Farm, and Brown Spot. Even with the most susceptible strain there was considerable variation ranging from one mouse in which all tissues were infectious to another in whom but a single brain site was positive. In general, the tissues in order of decreasing susceptibility were spleen, liver, brain, blood,

Table 2.—*Summary of mouse strain susceptibility to experimental syphilis (Nichols strain)*

[Indicated in the body of the table by mouse strain and by tissue are the proportion of mice and the proportion of inoculated sites that were positive.]

Strain	Spleen		Liver		Brain		Blood		Lymph Node		Muscle		Total		Percent mice positive in at least 1 site
	M[1]	S[2]	M[1]	S[2]	M[1]	S[2]	M[1]	S[2]	M[1]	S[2]	M[1]	S[2]	M[1]	S[2]	
CFW	9/10	35/50	8/10	26/50	8/10	28/50	4/10	8/50	3/10	3/50	3/10	3/50	35/60	103/300	100
CF-1	7/8	28/40	5/8	11/40	6/8	14/40	5/8	10/40	0/8	0/40	0/8	0/40	23/48	63/240	100
C_3H	7/10	13/50	4/10	6/50	6/10	15/50	1/10	2/50	1/10	1/50	1/10	1/50	20/60	38/300	90
CW	6/10	14/50	5/10	9/50	2/10	2/50	2/10	3/50	4/10	12/50	1/10	1/50	20/60	41/300	100
C57 black	7/10	12/50	5/10	5/50	3/10	9/50	1/10	1/50	0/10	0/50	0/10	0/50	16/60	27/300	80
Chocolate	4/10	4/50	5/10	6/50	1/10	2/50	2/10	2/50	4/10	13/50	0/10	0/50	16/60	27/300	80
dba-line 1	3/10	3/50	2/10	4/50	3/10	3/50	0/10	0/50	2/10	2/50	1/10	1/50	11/60	13/300	50
State Laboratory	1/10	1/50	1/10	1/50	5/10	13/50	1/10	1/50	0/10	0/50	1/10	1/50	9/60	17/300	50
Brown Spot	3/10	4/50	0/10	0/50	2/10	3/50	0/10	0/50	0/0	0/50	0/10	0/50	5/60	7/300	50
Total	47/88	114/440	35/88	68/440	36/88	89/440	16/88	27/440	14/88	31/440	7/88	7/440	155/528	336/2640	

[1] Number of mice positive. Number of mice tested.

[2] Number of sites positive. Number of sites tested.

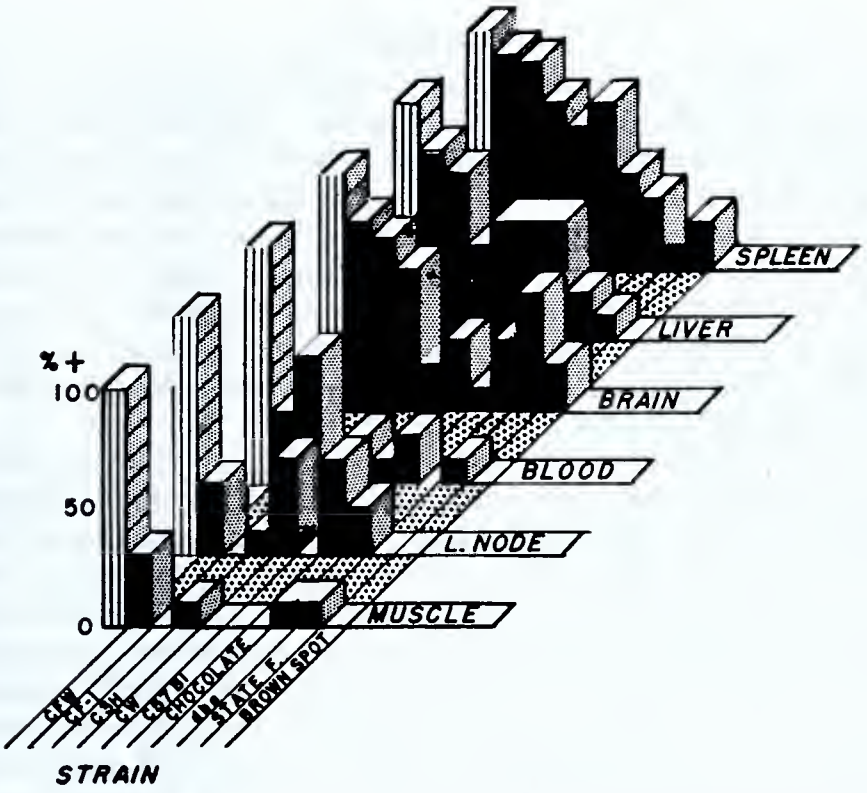


FIGURE 1.—Variations in the susceptibility of mouse strains to *Treponema pallidum* (Nichols strain). The relative infectiousness of six tissues from nine strains of mice is summarized. Shown is the percentage of each of these tissues giving a positive result at one or more of five intracutaneous rabbit sites.

lymph node, and muscle. The relative infectiousness of the tissues varied to some extent with the strains. Thus, the State Laboratory strain, which on the whole was rather resistant, showed 50 percent of the brains positive at the 4-week transfer time. Exceptions were frequent, and occasionally the most susceptible tissues were noninfectious while other organs in the same animal harbored the organism.

Had transfer tissue been inoculated intratesticularly rather than intracutaneously, a higher proportion of positive results might have been obtained. Earlier work (*7*) employing the Nichols strain from rabbit testicular emulsion has shown the minimal infectious intratesticular inoculum to be 1 to 2 spirochetes, while from 5 to 20 times as many organisms were required to produce infection by the intracutaneous route. Since some 2,500 rabbits would have been required to accomplish intratesticular inoculation in the present experiment, this method had to be abandoned in favor of the less sensitive technic. This difference in sensitivity may account for the more regular infectiousness of blood, spleen, and lymph nodes encountered by Rosahn and his coworkers (*10*).

Discussion

The search for a susceptible small animal host in which symptomatic syphilis would develop has motivated many of the studies of infection in the mouse. Such a host would afford considerable economy in materials and space for many types of study. Although the present experiments have not demonstrated such a host, they do indicate that within a single species there may be considerable variation in the susceptibility of different strains. Whether selective breeding among the more susceptible strains might further enhance their usefulness is still unknown and may well warrant further study.

Strain variation as here demonstrated differs from the pattern described by Pierce, Dubos, and Middlebrook (*6*) in experimental tuberculosis, in which the pigmented mouse strains were found to be more susceptible than the nonpigmented strains. With experimental syphilis no correlation was found between resistance to infection as here measured and pigmentation of the host.

That strain variation in susceptibility to syphilis may also extend to the rabbit has been indicated by two studies. Frazier and Mu (*11*) reported that of seven albino and eight brown rabbits inoculated with the Nichols strain of *T. pallidum,* the former developed a more intense orchitis of longer duration than the latter. The same group also showed a higher incidence of metastatic keratitis. Rosahn (*12*), by measuring the frequency, time of occurrence, and severity of metastatic lesions, concluded that the English, Himalayan, and Rex rabbits were more susceptible to syphilis than the Havana and Dutch breeds.

The reasons for these strain variations are, of course, as obscure as the reasons why only a few mammals are susceptible to syphilis. Whether such selectivity is an expression of natural immune mechanisms or whether they result from obscure variations in metabolic structure remains unanswered. The immediate importance is in the recognition of strain variations in the susceptibility of mice to experimental syphilis. Experiments employing this species as a host should allow for that factor.

Summary

1. Nine strains of the laboratory mouse (*Mus musculus*) were tested for susceptibility to infection with *T. pallidum* (Nichols strain) as measured by the infectiousness of their tissues for the rabbit on intracutaneous inoculation.

2. In order of decreasing susceptibility the strains were: CFW, CF-1, C_3H, CW, C-57 black, Chocolate, dba-line 1, State Laboratory, and Brown Spot.

3. None of the strains developed symptomatic infection.

4. In order of decreasing infectiousness the tissues were: spleen, liver, brain, blood, lymph node, and skeletal muscle.

5. There was wide individual variation in the infectiousness of tissues not only between strains of mice, but within the same strain.

References

1. KOLLE, W.; SCHLOSSBERGER, H.: Experimentelle Studien uber Syphilis und Rekurrensspirochetose V. Ueber symptomlose infection von Mausen und Ratten, sowie symptomlose superinfektionen syphilitischer Keninchen mit *Spirochaeta pallida*. Deutsche med. Wchnschr., 52: 1245, 1926.
2. GUEFT, B.; ROSAHN, P. D.: Experimental mouse syphilis, a critical review of the literature. Am. J. Syph., Gonor. & Ven. Dis., 32: 59, 1948.
3. JAHNEL, F.; SCHARRER, B.: Ein Beitrag zur Frage der Syphilisempfindlichkiet im Tierreich, imbesondere verschiedener Mousearten. Dermat. Ztschr., 71: 1, 1935.
4. WILE, U. J.; JOHNSON, S. A. M.: Experimental syphilis in different species of native American mice. Am. J. Syph., Gonor. & Ven. Dis., 29: 416, 1945.
5. JAHNEL, F.: Further studies in experimental syphilis. Am. J. Syph., Gonor., & Ven. Dis., 21: 18, 1937.
6. PIERCE, C.; DUBOS, R. J.; MIDDLEBROOK, G.: Infection of mice with mammalian tubercle bacilli grown in tween-albumin liquid medium. J. Exper. Med., 86: 159, 1947.
7. MAGNUSON, H. J.; EAGLE, H.; FLEISCHMAN, R.: The minimal infectious inoculum of *Spirochaeta pallida* (Nichols strain) and a consideration of its rate of multiplication in vivo. Am. J. Syph., Gonor. & Ven. Dis., 32: 1, 1948.
8. MAGNUSON, H. J.; ROSENAU, B. J.: The rate of development and degree of acquired immunity in experimental syphilis. Am. J. Syph., Gonor. & Ven. Dis., 32: 418, 1948.
9. MAGNUSON, H. J.; ROSENAU, B. J.: The treatment of asymptomatic neurosyphilis in the white mouse. J. Invest. Dermat., 11: 435, 1948.
10. ROSAHN, P. D.; GUEFT, B.; ROWE, C. L.: Experimental mouse syphilis. I. Organ distribution of the infectious agent. Am. J. Syph., Gonor. & Ven. Dis., 32: 327, 1948.
11. FRAZIER, C. N.; MU, J. W.: Variation of response to infection with *T. pallidum* between albino and brown breed of rabbit. Proc. Soc. Exper. Biol. & Med., 27: 243, 1930.
12. ROSAHN, P.: The reaction of standard breeds of rabbits to experimental syphilis. J. Exper. Med., 57: 907, 1933.

The Treatment of Early Syphilis with Three Injections of Penicillin and with One Injection of Penicillin[1]

R. D. Wright, F. P. Nicholson, J. F. Mahoney, and R. C. Arnold[2]

A one-injection therapy for syphilis has long been the goal of syphilologists. Recent developments in antisyphilitic research, combined with the newer, repository-type vehicles, have at last given hope that this goal has been achieved.

A brief review of the compiled observations of the past 6 years is essential to the understanding of the rationale which led to the utilization of a one-injection schedule.

First of all, the mechanism by which penicillin kills spirochetes has never been completely analyzed. It is assumed that the antibiotic interferes in some way with the reproductive capacity of the organism. Whether the spirochetes are more vulnerable during division and are then killed by penicillin, or whether penicillin prevents reproduction and allows the organism to "die of old age", as it were, is not clear. At any rate, it seems that the reproductive period of their life cycle may be most important as far as penicillin therapy is concerned.

It was demonstrated by Magnuson, Eagle and Fleischman (*1*), and again by Cumberland and Turner (*2*), that the average dividing time of one spirochete into two is probably about 30 to 33 hours. Animal and human studies (*3*) have shown that cures could be obtained with wide variations in aqueous penicillin schedules ranging from 12 hours to seven or more days. In this regard, it is significant that when syphilitic rabbits were treated with large amounts of aqueous penicillin for only 12 hours, a certain number of the animals were cured; conversely, when therapeutic penicillin levels were maintained in human syphilitic subjects for 72 hours, the vast majority were cured, as judged by adequate follow-up. These latter results are significantly the same as the results obtainable with 7 days of aqueous penicillin treatment administered in a similar manner. It is also of interest to note that 100 percent cure in syphilitic rabbits is not attained until therapeutic penicillin levels have been maintained for at least 72 hours (*3*).

Peters and Barton (*4*) treated a group of syphilitic patients with enormous dosages of penicillin ranging up to 25 million

---

[1] From the Venereal Disease Research Laboratory and the U. S. Marine Hospital, Staten Island, N. Y.

[2] Presented at the symposium—Recent Advances in the Study of the Venereal Diseases, 1949.

units, in 24 hours. The positive results of this study were discouraging, in that an average of approximately 50 percent was judged to be in need of re-treatment on the basis of relapse. Investigations at the Venereal Disease Research Laboratory and the U. S. Marine Hospital, Staten Island, have shown that high penicillin levels in the blood serum, maintained for 48 hours, result in a relapse rate of about 10 percent (*5*). Two concepts, then, emerged from these studies as a working basis for future research: first, the time factor is of the utmost importance in the time-dose relationship; and, second, therapeutic penicillin blood levels must be maintained for at least 72 hours to assure maximum cure rates.

With the advent of procaine penicillin G in oil, a series of patients was studied to determine the duration of the levels obtainable with a single injection of 300,000 units of the drug. From the earliest clinical trials (*5*), it was discovered that although almost 100 percent of the patients exhibited therapeutic blood levels at the end of 24 hours, only 50 percent had detectable levels at the end of 36 hours.

Further study on the results of administration of larger amounts of the drug was contemplated, but this research was abandoned with the appearance of procaine penicillin G in oil with 2 percent aluminum monostearate on a weight by volume basis. Throughout the remainder of this paper the term "propenalate" will be used to designate microcrystalline procaine penicillin G in oil with 2 percent aluminum monostearate on a weight by volume basis.

Intensive study was undertaken to determine the predictable results of the administration of varying amounts of propenalate. Instead of presenting the laboratory results in their chronological order, they will be alluded to concurrently with the various schedules presented.

The first treatment schedule to be employed utilized three injections of propenalate: 600,000 units were administered each day for 3 days. The patients were unselected, except that all were patients who presented themselves with their first syphilitic infection in an untreated state, and all were darkfield positive. There were 94 patients in the group treated with this schedule; 64 had primary syphilis and 30 had manifestations of the secondary stages of the disease. Follow-up observations were obtained on 75 of these patients at various time periods ranging from 2 to 11 months. Sixty-seven of the 75 observed patients are at present showing satisfactory progress toward seronegativity or have reached the negative status as reflected by a battery

of tests. Eight patients so far have been in need of re-treatment, seven of whom have been classified by the clinical staff as being reinfected. One patient who originally had had secondary syphilis, was observed to have suffered an apparent serorelapse during the fifth posttreatment month. No clinical signs of syphilis appeared in the 2½ months during which he was observed before re-treatment. Following re-treatment with the same dosage of propenalate, the serologic pattern has been declining toward negativity.

In this connection it may be important to state that studies are now in progress at the Venereal Disease Research Laboratory to determine whether any diagnostic significance may be attached to therapeutic results following re-treatment with the same schedule and the same lot number. In other words, attempts are being made to ascertain whether a true relapse will relapse a second time when re-treated with the same schedule of penicillin, or whether a favorable result following the administration of a second, identical course of therapy may indicate an asymptomatic reinfection.

Figure 1 reveals the average penicillin blood levels obtained in a group of 69 patients treated with propenalate, 600,000 units every day for 3 days. As can be seen, although 100 percent of the patients maintained average levels of 0.306 unit per cubic centimeter of serum through the 72-hour period, almost 90 percent showed an average level of 0.166 unit per cubic centimeter of serum 96 hours after the initial injection.

The second treatment schedule to be presented utilized one injection of 900,000 units of propenalate. Nineteen patients were placed on this schedule, 12 of whom have been observed for 4 months or longer. Eleven of the 12 have shown satisfactory clinical and serologic progress, but one has been re-treated on the basis of a clinical relapse which occurred in the third month following therapy. He also, following re-treatment with an identical schedule, has been showing satisfactory progress.

Figure 2 reveals the average serum penicillin levels obtained in a group of patients treated with propenalate—one injection of 900,000 units. It can be seen that all patients maintained average blood levels of 0.153 unit per cubic centimeter through the 72-hour period, although the average level was approximately one-half that obtained in patients who were given 600,000 units of propenalate every day for 3 days.

Figure 3 shows the average serum levels obtained in 98 patients who were given one injection of 600,000 units of propenalate for

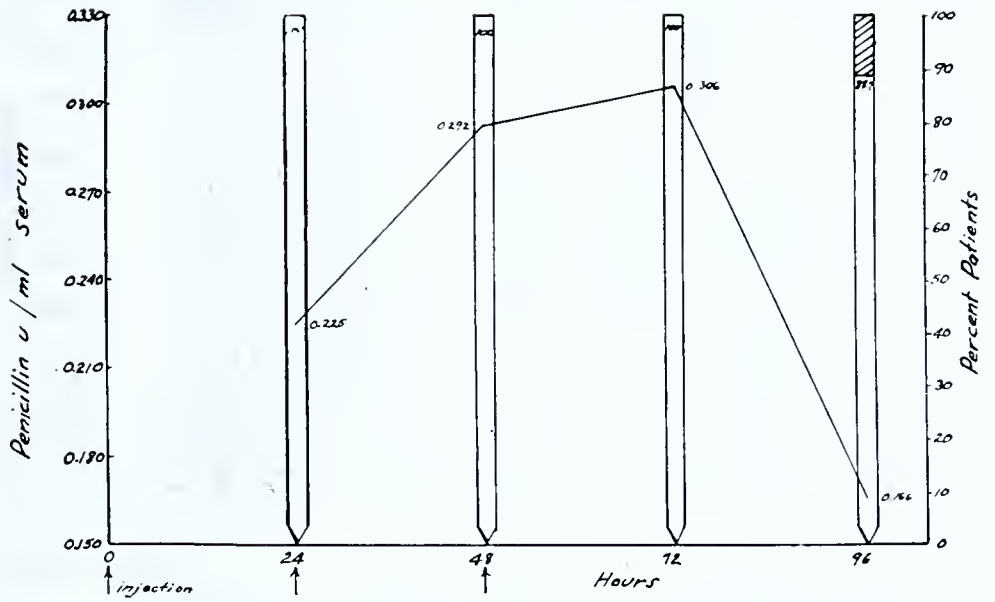


FIGURE 1.—Procaine penicillin G in peanut oil containing 2 percent (w/v) aluminum monostearate. Dosage schedule—600,000 units q. 24 hours x 3. (69 patients.)

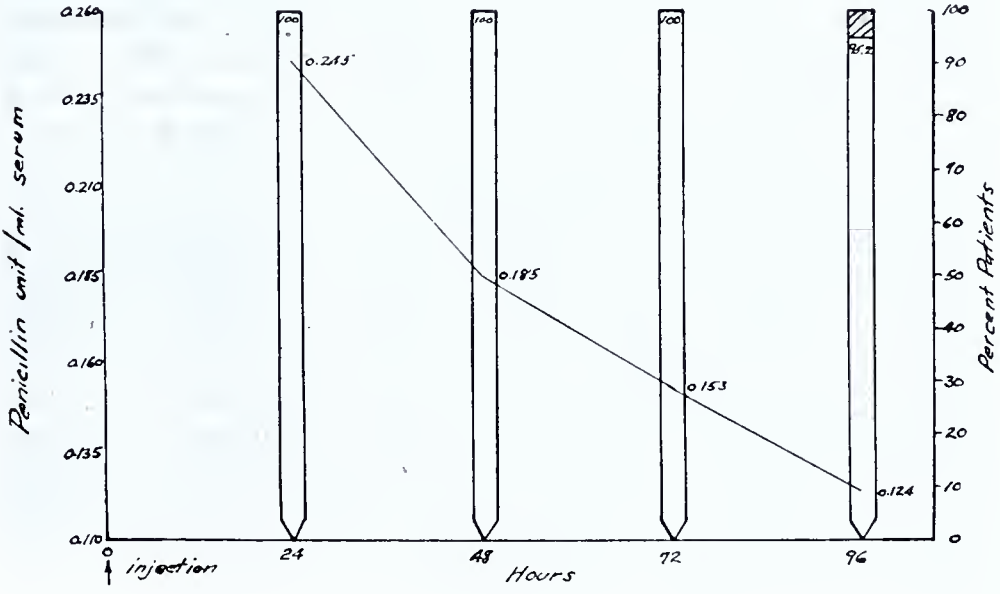


FIGURE 2.—Procaine penicillin G in peanut oil containing 2 percent (w/v) aluminum monostearate. Dosage schedule—900,000 units q. 24 hours x 1. (21 patients.)

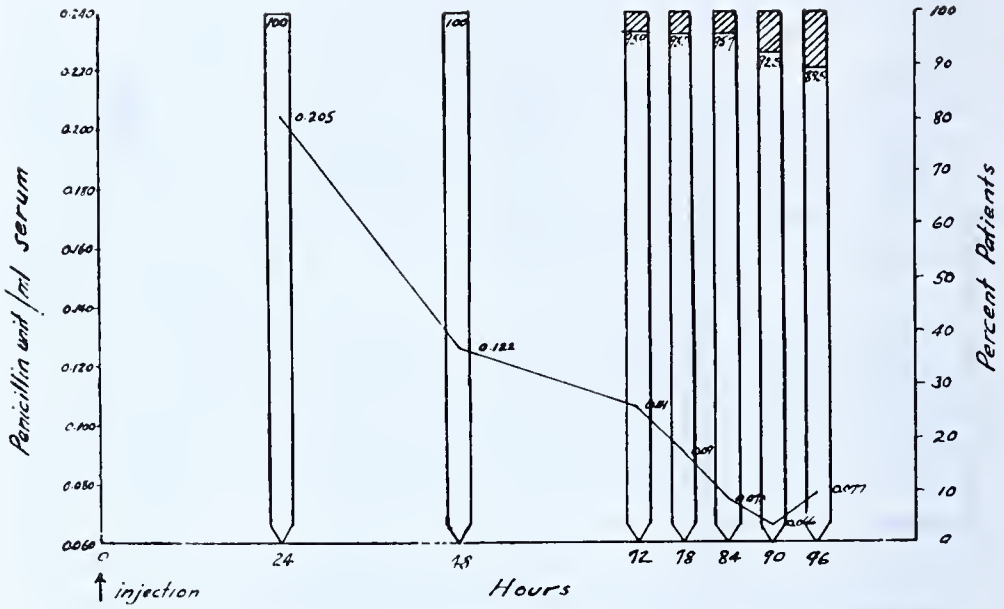


FIGURE 3.—Procaine penicillin G in peanut oil containing 2 percent (w/v) aluminum monostearate. Dosage schedule—600,000 units q. 24 hours x 1. (98 patients.)

level determinations. It can be seen that, as the individual dose is lowered, a rare patient will fail to maintain a detectable level of 0.0125 unit per cubic centimeter of serum for 72 hours. At this point it may be important to note that, in the light of past experience with aqueous penicillin, approximately 90 percent of the patients who maintain penicillin levels for only 48 hours will exhibit satisfactory clinical and serologic results. Thus, even in those patients in whom one injection of propenalate lacks a few hours of maintaining a 72-hour level, one should expect to have a fairly high percentage of cures.

Finally, a schedule was undertaken in which one injection of propenalate, consisting of 300,000 units, was administered to a group of patients who had early syphilis. As of the time of writing, 88 patients with primary or secondary syphilis have been treated with this schedule. Since this form of therapy is still being studied at the Venereal Disease Research Laboratory and since not enough time has elapsed to permit adequate follow-up, suffice it to say that of the 55 patients who have been observed for at least 3 months, one patient has suffered a mucocutaneous relapse, two have been classed as apparent serologic relapses, and one has been judged to be reinfected.

Figure 4 shows the average concentration of penicillin in the sera of 173 patients studied. At 72 hours, more than 95 percent of these patients showed a detectable level of penicillin in the blood serum.

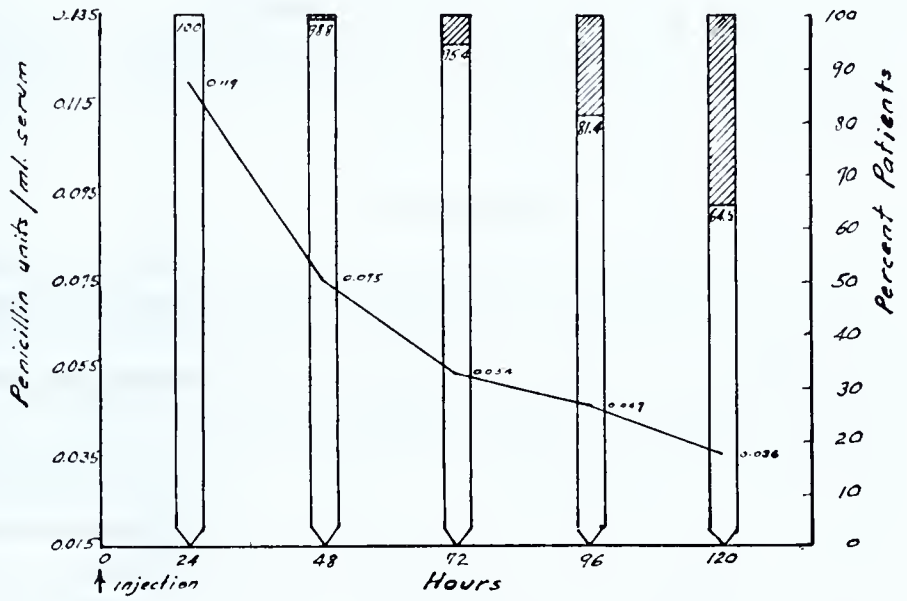


FIGURE 4.—Procaine penicillin G in peanut oil containing 2 percent (w/v) aluminum monostearate. Dosage schedule—300,000 units q. 24 hours x 1. (173 patients.)

Summary

It is felt that one injection of propenalate is enough to cure early syphilis in the great majority of cases. It is desired to emphasize that no specific amount of propenalate is recommended at this time for the one-injection treatment of early syphilis. The true therapeutic effect and the definitive dosage of propenalate or other antibiotics remain to be determined.

Also, it is expected that better compounds will probably be developed which will enable penicillin to be absorbed and eliminated even more slowly than propenalate. Should this occur, the basis in theory and in practice for a one-injection therapy of early syphilis would be fortified.

Conclusions

1. Seventy-two hours of therapeutic penicillin serum levels achieve as great a cure-rate when used in the treatment of early syphilis as do 7 days of therapeutic levels.

2. A schedule employing three daily injections of 600,000 units of propenalate compares favorably in therapeutic results with the 3- and the 7-day aqueous penicillin schedules.

3. A tentative schedule employing a single injection of 300,000 units of propenalate gives promise of a satisfactory cure-rate in early syphilis.

References

1. Magnuson, H. J.; Eagle, H.; Fleischman, R.: The minimal infectious inoculum of *Spirochoeta pallida* (Nichols strain), and a consideration of its rate of multiplication in vivo. Am. J. Syph., Gonor. & Ven. Dis., 32: 1, 1948.
2. Cumberland, M. C.; Turner, T. B.: The rate of multiplication of *Treponema pallidum* in normal and immune rabbits. Recent Advances in the Study of Venereal Diseases, a Symposium, 1948.
3. Arnold, R. C.; Mahoney, J. F.; Nicholson, F. P.; Wright, R. D.: Penicillin therapy of early syphilis. IV. J. Ven. Dis. Inform., 30: 125-127, May 1949.
4. Peters, E. E.; Barton, R. L.: The massive intravenous therapy of early syphilis. Am. J. Syph., Gonor., & Ven. Dis., 31: 5, 1947.
5. Thayer, J. D.; Bucca, M. A.; Walker, A. I.: Penicillin blood and spinal fluid levels, developed in man by various schedules of aqueous and repository penicillins. To be published.

Treatment of the Syphilitic Pregnant Woman with Penicillin in Absorption-Delaying Vehicles [1]

Norman R. Ingraham, Jr., Elizabeth Kirk Rose, and Herman Beerman

The purpose of this paper is to bring up to date the description of the report of our experience with the prevention of congenital syphilis by treatment of the syphilitic pregnant woman with penicillin in absorption-delaying vehicles. This work was commenced

[1] From the Institute for the Study of Venereal Disease, University of Pennsylvania, with the cooperation of the U. S. Public Health Service. The Departments of Dermatology and Syphilology, and of Pediatrics, School of Medicine and Graduate School of Medicine, University of Pennsylvania; the Division of Venereal Disease Control, Department of Public Health of Philadelphia; the Division of Dermato-Syphilology, Philadelphia General Hospital; and the Department of Dermatology and Syphilology, Pennsylvania Hospital, are represented in the authorship. Assisted by the Squibb Fellowship in Chemotherapeutic Research.

in October 1945. In the 1947 symposium (*1*) we reported on 46 cases treated with the old amorphous calcium penicillin unstandardized as to particle size. In this group two living syphilitic infants were born and one has since been discovered. We have continued this work with crystalline G penicillin in oil beeswax standardized as to particle size and more recently with procaine penicillin in oil and have increased our series to 111 cases with the birth of no additional syphilitic infants. It would accordingly seem that standardization of the absorption-delaying vehicles to produce dependable prolonged blood levels has largely solved the problem of preventing passage of treponemes to the fetus or even of treating in utero the already infected fetus.

In performing this work we have exercised three types of clinical statistical controls. First, we have determined the incidence of fetal mishaps in a comparable group of nonsyphilitic pregnant women. Secondly, we have determined the outcome of pregnancy in a comparable group of syphilitic pregnant women who have remained untreated during pregnancy. Thirdly, since the reports in the literature to date are largely concerned with the treatment of the pregnant woman for syphilis with penicillin in aqueous solution by frequent injection, we have expanded our own aqueous penicillin group to give comparable current material for comparison.

During the period 1945 to 1948, among 4,902 nonsyphilitic deliveries at the Philadelphia General Hospital, from which 34 percent of this material was drawn, 87.6 percent normal fullterm living infants resulted. There were 0.8 percent stillbirths and 3 percent neonatal deaths. The remainder were classified as premature (2.9 percent) or miscarriages (5.7 percent). Some abnormal termination of the pregnancy is to be anticipated in a little over 12 percent of the type of patients with whom we are dealing, without any consideration of syphilis.

It is a sad commentary, perhaps, on the gap which still exists between the theoretical and the ideal, in spite of public health interest and the enactment of premarital and prenatal examination laws, that in the same period it was possible to collect 75 syphilitic women who delivered without receiving any antisyphilitic treatment whatever, either before or during their pregnancies.[2] As in many similar municipal hospitals, the percentage of unregistered mothers who deliver at the Philadelphia General Hospital without prenatal care is still high. Of these 75 syphilitic women, 7 had primary or secondary syphilis: 4 living syphilitic

[2] This analysis is from as yet unpublished data compiled from Philadelphia General Hospital material by V. S. Wammock, M.D.; O. M. Carrozzino, M.D., M.P.H.; N. R. Ingraham, Jr., M.D.; and Nellie Clair, R.N.

infants resulted, 1 neonatal death and 2 stillbirths. Not a single normal infant occurred. Fifty-four of the seventy-five cases were diagnosed latent and could be reasonably classified as early. Among these there were 31 percent living syphilitic infants, 17 percent stillbirths, 6 percent neonatal deaths, and 29 percent normal full-term living infants. In addition 8 percent were premature infants and 9 percent miscarriages. Fourteen of the 75 cases could be reasonably classified as late syphilis and pregnancy. With these, 93 percent normal living infants resulted. Accordingly, review of a comparable group of untreated syphilitic pregnant women coming to term during the period of this study indicates that there was apparently no chance of a normal infant if the woman developed primary or secondary syphilis during pregnancy, there was a slight chance of having a normal infant with early latent syphilis, but with late syphilis the possibility of having a normal infant, even without treatment, was apparently good. The value of treatment is best shown during the invasive stages of the disease when the organisms of syphilis gain frequent access to the maternal blood stream.

In proceeding to the third type of clinical control in which the two principal types of penicillin therapy are compared, we would first like to show that the group of women treated with aqueous penicillin is roughly comparable to those treated with penicillin in absorption-delaying vehicles (table I). Both groups are predominantly Negro; are largely early syphilis, about one-third of the women having infectious lesions during the pregnancy; and have been treated in all stages of the pregnancy, about one-fifth after the thirty-second week, when the probability of infection of the fetus is greatest.

Table 1.—*Syphilitic pregnant women treated with penicillin; comparative statistical data in percent on material used, analyzed by type of treatment*

Type of penicillin used	Number of pregnancies	Race		Stage of disease			Week in pregnancy when treatment was commenced			
		White	Negro	Early symptomatic	Early latent	Late	1–15	16–23	24–31	32–40
		Percent	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*
Aqueous	132	13	87	35	36	29	13	26	36	25
In absorption-delaying vehicle	111	7	93	28	48	24	21	31	29	19

With the aqueous penicillin group all syphilitic infants (2 in number) have appeared when a total dosage of less than 2.4 million units of penicillin was employed (see table 2). This

Table 2.—*Outcome of pregnancy analyzed in percent according to type of therapy given to syphilitic pregnant woman*

Type of penicillin used	Number of infants delivered	Outcome						
		Unsatisfactory			Living infants		Living infants syphilitic (less than 2.4 aqueous; amorphous Ca. P.O.B.)	Living infants syphilitic (2.4 or more aqueous; standardized delayed absorption)
		Miscarriage	Stillbirth	Neonatal death	Normal	Syphilitic		
Aqueous	134	2.3	0.8	0.8	94.6	1.5	14	None (113 infants).
In absorption-delaying vehicle	113	0.0	4.5	3.6	89.2	2.7	6.4	None (62 infants).

represents two infants among 14 mothers, or a percentage failure rate of 14. There have been no syphilitic infants among 113 living offspring when total dosage of 2.4 million units or more of aqueous penicillin was employed. Our present aqueous penicillin schedule for the pregnant woman is 40,000 units every 2 hours for 90 injections, or a total 3.6 million units.

With penicillin in absorption-delaying vehicles all three living syphilitic infants occurred among pregnancies in which the old unstandardized amorphous calcium penicillin in oil beeswax was employed; a failure rate of 6.4 percent (see table 2). With the standardized penicillin preparations with absorption-delaying vehicles, not a single syphilitic infant has resulted among the 62 living offspring of syphilitic pregnancies. Our standard course for penicillin in absorption-delaying vehicles is 600,000 units once daily for 8 days, totaling 4.8 million units. We are not yet prepared to report on material in which the interval between injections is greater than 24 hours.

Provided adequate penicillin dosage is employed, it would accordingly seem to make very little difference whether it is given by frequent injection in aqueous solution or once daily in an absorption-delaying vehicle. In fact, when proper treatment is employed the expectancy of full-term normal infants seems to be greater among the syphilitic groups (89.2 and 96.4 percent, respectively) than it is among the nonsyphilitic control group (87.6 percent).

Our work continues to show that amounts of penicillin insufficient to effect complete clinical and serologic cure of the mother of her syphilis are nonetheless sufficient to result in the birth of a normal infant (table 3). An analysis of our two groups show that approximately 79 percent of the aqueous penicillin group were seropositive at delivery compared to 86 percent for the

Table 3.—*Response of the syphilitic mother following penicillin therapy during pregnancy, analyzed according to type of treatment*

Type of penicillin used	Number of mothers followed	Clinical relapses	Reinfections	Serologic response of mothers				
				Seropositive at delivery	Seronegative at end of observation	Seronegative at end of observation, by diagnostic groups		
						Early symptomatic	Early latent	Late
		Percent	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*
Aqueous	132	3.8	2.3	78.8	46.2	60.9	47.9	26.3
In absorption-delaying vehicle	[1] 110	2.7	0.0	86.3	40.9	67.7	35.9	18.5

[1] One mother died immediately after delivery, of causes unrelated to penicillin therapy or syphilis and is thus exeluded from this table.

delayed-absorption group. At the end of observation only 46.2 percent of the aqueous penicillin group of mothers had become seronegative. This percentage for the delayed-absorption penicillin group was 40.9. In the aqueous penicillin group there were five infectious relapses among 132 patients. Three additional instances seemed justifiably classified as reinfections on the basis of the evidence in hand. There were three infectious relapses among 110 cases in the delayed-absorption penicillin group.

In addition to the cases just discussed, treated with penicillin during pregnancy, we have now adequately followed 130 patients in whom penicillin was given for syphilis prior to pregnancy or during a preceding pregnancy but withheld during the current pregnancy because the expectant mother was responding nor-

Table 4.—*Penicillin treatment for syphilis prior to pregnancy; no specific treatment during pregnancy, analyzed as to type of therapy and stage of disease when treated*

Type of penicillin used	Total pregnancies	Total living syphilitic infants	Miscarriages, stillbirths, neonatal deaths	Mothers seropositive at delivery	Stage of syphilis for which originally treated			Period post penicillin at which delivery occurred			Average period post penicillin when delivery occurred
					Symptomatic early	Early latent	Late	< 1 yr.	1–2 yrs.	> 2 yrs.	
	Number	*Number*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Months*
Aqueous	92	0	12.0	31.5	42.2	55.2	2.6	20.8	46.7	32.5	21.4
In absorption-delaying vehicle	38	0	2.6	34.2	75.0	17.4	7.6	15.8	63.1	21.1	20.0

mally. Ninety-two of these women were treated with aqueous penicillin, 38 with penicillin in absorption-delaying vehicles. Not a single syphilitic living infant has resulted. An analysis of these groups by percentage occurrence of fetal mishap, serologic status of the mother at the time of delivery, period post penicillin when birth occurred, and stage of the disease when treatment was given is shown in table 4. More than 90 percent of the mothers had been treated for symptomatic or latent early syphilis. About one-third were still seropositive at delivery. Since no syphilitic infants have resulted there is no difference in outcome when related to the type of penicillin, aqueous or delayed absorption, employed.

Summary and Conclusions

1. Provided penicillin dosage is adequate, treatment of the pregnant woman with early syphilis to prevent congenital syphilis may be equally well accomplished with either aqueous penicillin or penicillin in absorption delaying vehicles.

2. For aqueous preparations dosage of crystalline G penicillin in excess of 2.4 million Oxford units over a period of 7 to 8 days seems satisfactory to protect the infant.

3. For penicillin in absorption delaying vehicles a total dosage of 4.8 million units or more given in equally divided doses once daily over a period of 8 days seems satisfactory to protect the infant. These must be standardized preparations capable of giving definite blood and tissue levels for 24 hours or more.

4. Failures in protecting the infant have resulted from smaller dosage than above recommended of either the aqueous or delayed absorption preparations. They have also occurred and will continue to occur in those cases in which the fetus is diseased beyond hope when the treatment is commenced late in the pregnancy.

5. Ideal application of penicillin treatment either before or during pregnancy gives results approaching perfection in the prevention of infantile congenital syphilis, and in this study has caused a higher percentage of normal living infants among the syphilitic than among the nonsyphilitic group when the comparable vital statistics were considered for the obstetrical service as a whole.

References

1. Ingraham, N. R., Jr.; Rose, E. K.; Beerman, H.; Wammock, V. S.; Stokes, J. H.; Gyorgy, P.: Treatment of the syphilitic pregnant woman with penicillin in oil beeswax: A comparison with results obtained using aqueous sodium penicillin. J. Ven. Dis. Inform., 28: 155–161, Aug. 1947.

Report from Central Statistical Unit on Comparative Failure Rates for Early Syphilis Treated with Penicillin [1]

Margaret Merrell

Introduction

The Central Statistical Unit is closing its studies this spring on the comparison of failure rates for different treatment schedules. In connection with the completion of this phase of the study a final report is being prepared on the various questions which the study was designed to answer. This morning I am going to present a few points from this report.

Penicillin G

I want first to report on the schedules involving penicillin G. This study was designed to settle just two issues, the relative merits of a total dose of 2.4 vs. 4.8 million units, and the merits of an interval of 2 hours vs. 3 hours. There were consequently just 4 schedules of treatment, all treatments extending over 7.5 days. One treatment involved a total of 2.4 million units, with injections every 2 hours (i.e., approximately 27,000 units per dose for 90 doses) ; a second treatment involved a total of 2.4 million units with injections every 3 hours (40,000 units per dose, 60 doses). The other two involved just twice as much per dose.

This study seems to me more satisfactory in its set-up than any other phase of the Nation-wide study. The fact that only two issues instead of a battery were under investigation meant that the material was not fractionated so many ways. There were about 3,000 cases, of which over two-thirds were concentrated at three large clinics which distributed their cases almost equally over the 4 schedules. Thus the cases under these 4 treatments were almost identical in their distribution as to color, sex, and admission diagnosis. About 60 percent were early secondary, 25 percent seropositive primary, and 15 percent seronegative primary. Males were slightly more numerous than females and there were about 3 times as many colored as white.

Thus, in comparing the 4 schedules for all cases, we are comparing similar distributions of cases for the different schedules even though we do not have specific diagnostic groups separated out. At the various stages of follow-up essentially the same dis-

[1] From the Department of Biostatistics, the Johns Hopkins University School of Hygiene and Public Health.

tribution remains as at the start, which suggests that the cases lost from follow-up are not highly selective.

We have computed failure rates based on first failures (i.e. serologic or clinical), and on clinical failures only.

Figure 1 shows cumulative failure rates for all failures, whether serologic or clinical, for the 4 schedules, the rates being carried to 2 years after treatment. The four schedules show rates which crisscross back and forth and never show any appreciable difference. At 1 year they range from 9 to 10 percent failure, at 2 years from 11 to 13 percent. These rates are as close together as rates on four groups would be expected to be if the treatments had been identical in effect. If we look at the effect of doubling the dose we see that in one case the higher dose came out with a higher failure rate, in the other case with a lower rate, but the differences are quite trivial. Similar size differences are characteristic of the 2- and 3-hour interval comparisons.

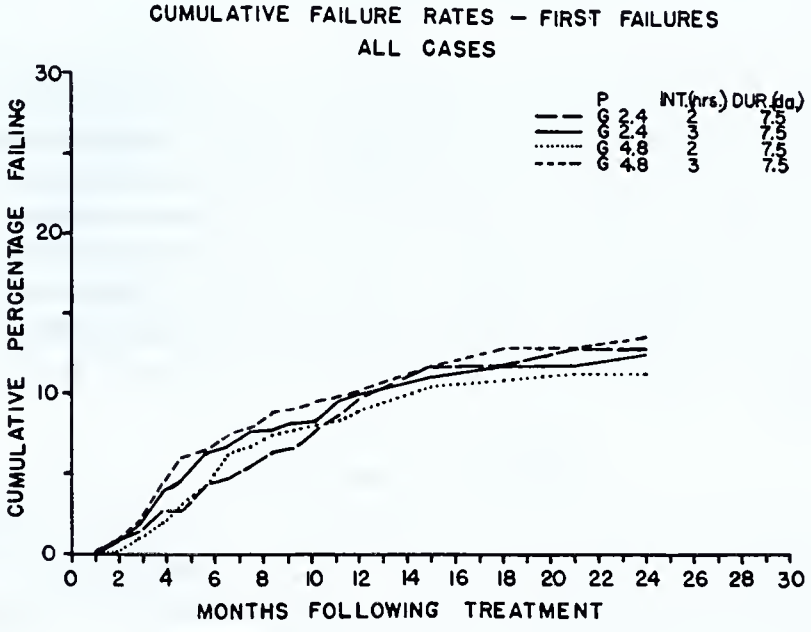


FIGURE 1.

If now we turn to the clinical failures only, we find in figure 2 essentially the same picture, but with slightly lower rates, since those cases that were designated as failures solely on the serologic evidence are considered successes in this classification. Here at 1 year, the rates vary from 8 to 9 percent and at 2 years from 9 to 10 percent. At 10 months three of the four rates are identical at 7 percent and the fourth is 9 percent. At 2 years they are only 1 percent apart.

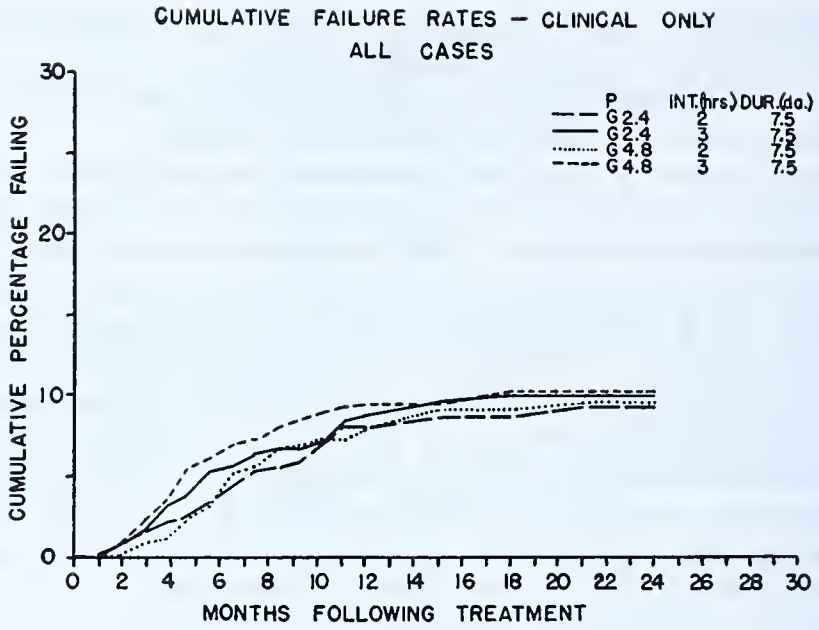


FIGURE 2.

From this evidence it seems justified to conclude that there is nothing to be gained by stepping the dose up from 2.4 to 4.8 million units, that whatever penicillin can do is being done at the lower dose. Also, as far as failure rates are concerned, it is unimportant whether an interval of 2 or 3 hours is used. This point might as well be decided on other grounds such as administrative convenience et cetera. The rates for these treatments seem quite favorable, 10 percent for clinical failures at 2 years, and about 12 percent for all failures, clinical and serologic, at this time.

Subgroup Comparisons

Although comparison of these schedules with various schedules of amorphous penicillin may be a little academic now, I have prepared some graphs for a few of the subgroups of cases to indicate the general level of these comparisons.

Figure 3 shows for white males two schedules of amorphous penicillin, 1.2 and 2.4 million units, respectively, and a combined penicillin and metal schedule (1.2 million P, 320 mg. As, and 0.6 gm. Bi). These are compared with the combined G schedules. There are also the combined G schedules for white females. At 12 months the G schedules and the combined amorphous penicillin and metal therapy have failure rates of 5 percent, compared with 8 to 9 percent for amorphous penicillin alone in the doses tested here. Although the numbers are not very large, this sort of

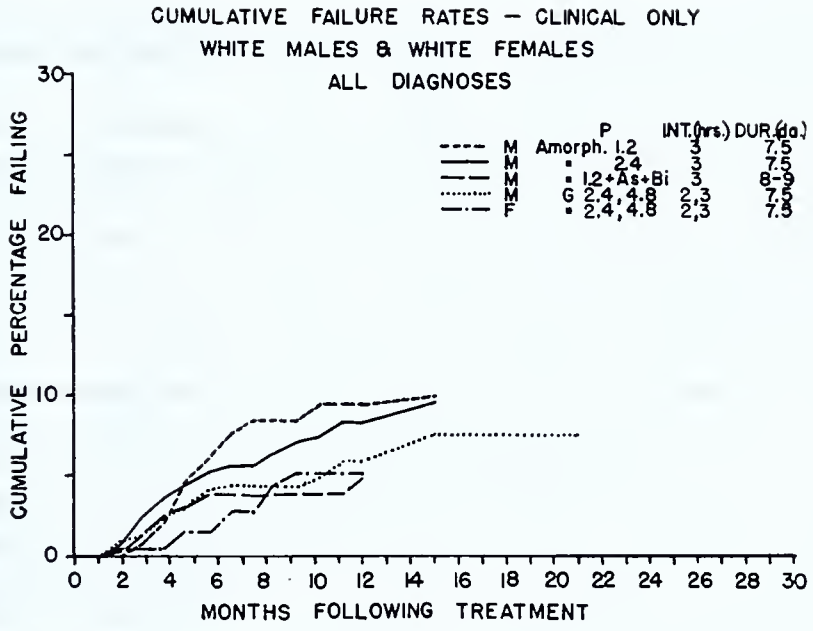

CUMULATIVE FAILURE RATES — CLINICAL ONLY
WHITE MALES & WHITE FEMALES
ALL DIAGNOSES
CUMULATIVE PERCENTAGE FAILING
MONTHS FOLLOWING TREATMENT
P INT.(hrs.) DUR.(da.)
M Amorph. 1.2 3 7.5
M " 2.4 3 7.5
M " 1.2+As+Bi 3 8-9
M G 2.4, 4.8 2,3 7.5
F " 2.4, 4.8 2,3 7.5

FIGURE 3.

result is seen in several of the other specific groups, which seems to give it some validity, namely that the G schedules and the combined penicillin and metal therapy have more favorable rates than amorphous penicillin alone.

Turning to one of the Negro comparisons, figure 4 shows, for early secondary syphilis in Negro males, essentially the same results, with the Negro rates being a shade higher than the white.

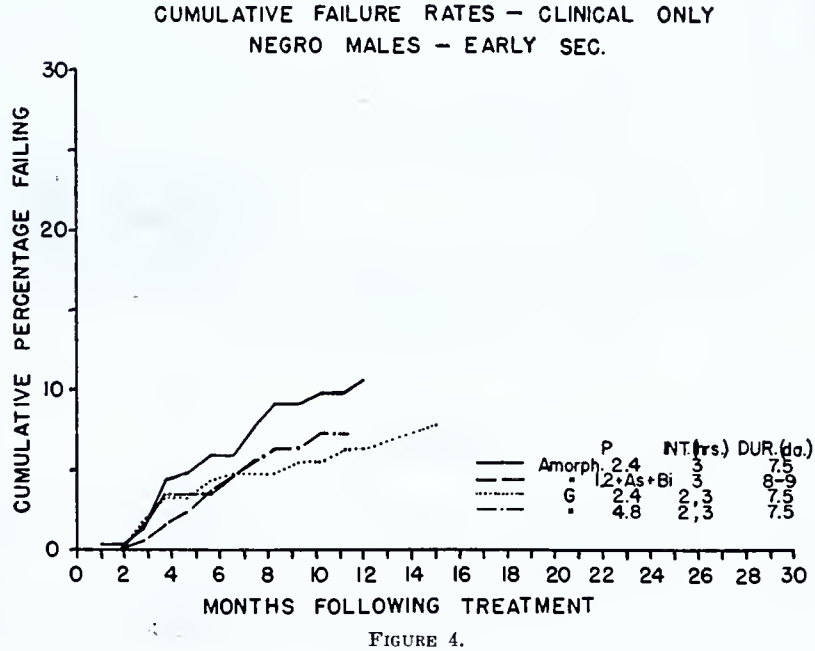

CUMULATIVE FAILURE RATES — CLINICAL ONLY
NEGRO MALES — EARLY SEC.
CUMULATIVE PERCENTAGE FAILING
MONTHS FOLLOWING TREATMENT
P INT.(hrs.) DUR.(da.)
Amorph. 2.4 3 7.5
" 1.2+As+Bi 3 8-9
G 2.4 2,3 7.5
" 4.8 2,3 7.5

FIGURE 4.

The primary positive Negro males (not shown here) have somewhat higher rates than the secondary but with the comparisons between schedules about the same.

In order to eliminate the factor of clinic variation in results, I want to show a final comparison for a single clinic. Figure 5 shows four of the schedules used by Bellevue Hospital. The distribution of cases on these schedules was quite similar, and we have the advantage of similarity of follow-up procedures and criteria of failure associated with a single clinic's work. It is seen that the three schedules involving 2.4 million units of penicillin G, 4.8 million units of penicillin G, and that combining 2.4 million units of amorphous penicillin with 320 mg. As and 0.6 gm. Bi have the same rates, about 10 percent at a year, and not much increase at 2 years, while the schedule involving 0.6 million has a 17-percent failure rate at a year and 22 percent at 2 years. This schedule constitutes a type of control for us, to indicate that the results we are getting in the more successful treatments are actually associated with the treatments.

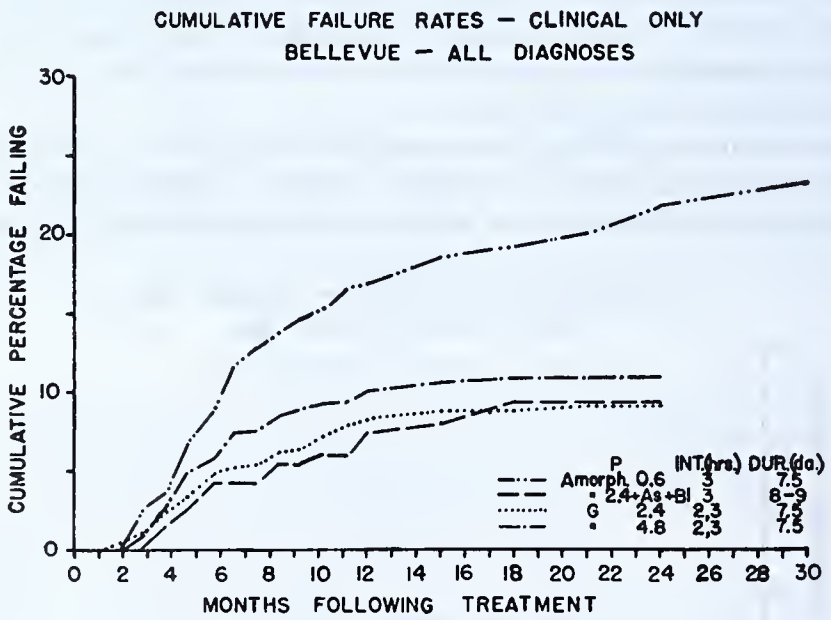


FIGURE 5.

Summary

At the close of this phase of our study I feel that the study has yielded some real results in that from the earlier trials we have been led to increasingly successful schedules of treatment. Although many of the questions originally asked are not settled,

it is now clear that with penicillin alone it is not necessary to go beyond 2.4 million units to achieve the maximum effect for the kind of schedules studied and that the precise timing of this is not a highly important issue. Some of the other issues that have been examined will be presented in detail in the more complete report.

Association of Course of Serologic Response and Clinical Outcome in Early Syphilis Treated with Penicillin[1]

R. V. Rider, M. T. Hoekenga, and M. S. Buerk

In his monograph, *Penicillin in Syphilis*, Moore presented charts representing 10 different types of blood serologic response after the penicillin treatment of early syphilis, which, he might have added, are typical of serologic response after metal chemotherapy as well. Moore speculated as to the probable clinical implications of these several types of serologic response, i.e., as to their relationship to "cure" or to impending clinical relapse. He felt that immediate serologic response, that is, response within the first year, might serve as a guide to the physician in these respects and, hence, as to the possible need for re-treatment.

The purpose of this paper is to examine Moore's assumptions in detail, especially as to the probability of clinical relapse.

This study is based on the records of about 23,000 cases of early syphilis which were available in the files of the Central Statistical Unit at the time the study was initiated. In our analysis we shall not compare treatment schedules, nor study the effect of factors such as race and sex. A preliminary survey of the material indicated that neither the dosage nor the race-sex factors are significantly influencing failure rates when the cases are grouped according to the defined serologic patterns.

It might be pointed out at the outset that as to "cure" of early syphilis by means of penicillin treatment, our material does not provide an answer to the question, "Does maintained seronegativity over the first few years after treatment signify cure?" Many more years of observation will be required to settle this point.

[1] From the School of Hygiene and Public Health, the Johns Hopkins University, and the Johns Hopkins Hospital.

In order to make the comparison of serologic with immediate clinical results, the cases were first examined as to their serologic behavior. From the 23,000 cases, 16,150 were selected for the analysis of serologic pattern. The omission of the remaining 7,000 cases was due to the inadequacy of the titered tests for syphilis, the tests being inadequate for this study either because of insufficient continuity of observation, or insufficient range of observation time. Otherwise, the omitted cases appeared to be a cross section of the entire 23,000.

As one might suppose, the range of observation time required to make a serologic classification varies with the serologic pattern. It seems likely that this might influence the cumulative failure rates observed. The differences in time were not great, however, and examination of them suggests that the bias they have introduced, if any, is in the direction of making even more significant the differences in failure rate which we shall suggest are important.

The 16,150 cases, then, were subdivided into 5 groups, as follows:

Group I is a combination of Moore's curves 1 and 2. Thus, group I is made up of cases of seronegative primary syphilis with no serorelapse during the first posttreatment year. In the schematic diagrams which will illustrate these five groups the vertical line represents the STS titer. This is arbitrarily shown in range 0 to 100 to distinguish between high- and low-titer tests. The horizontal line indicates time after treatment, the length of the line representing 1 year.

Of all cases of seronegative primary syphilis these 1,742 of group I form about 92 percent.

Only the remaining 8 percent of seronegative primary syphilis were observed to show serorelapse in the first posttreatment year.

Group II is composed of cases of seropositive early syphilis, becoming seronegative within 1 year of treatment, remaining so for at least 1 month, and showing no rise in titer during the first posttreatment year. The 7,380 cases in this group correspond with Moore's curve 3. Of all seropositive cases this group represents only about half.

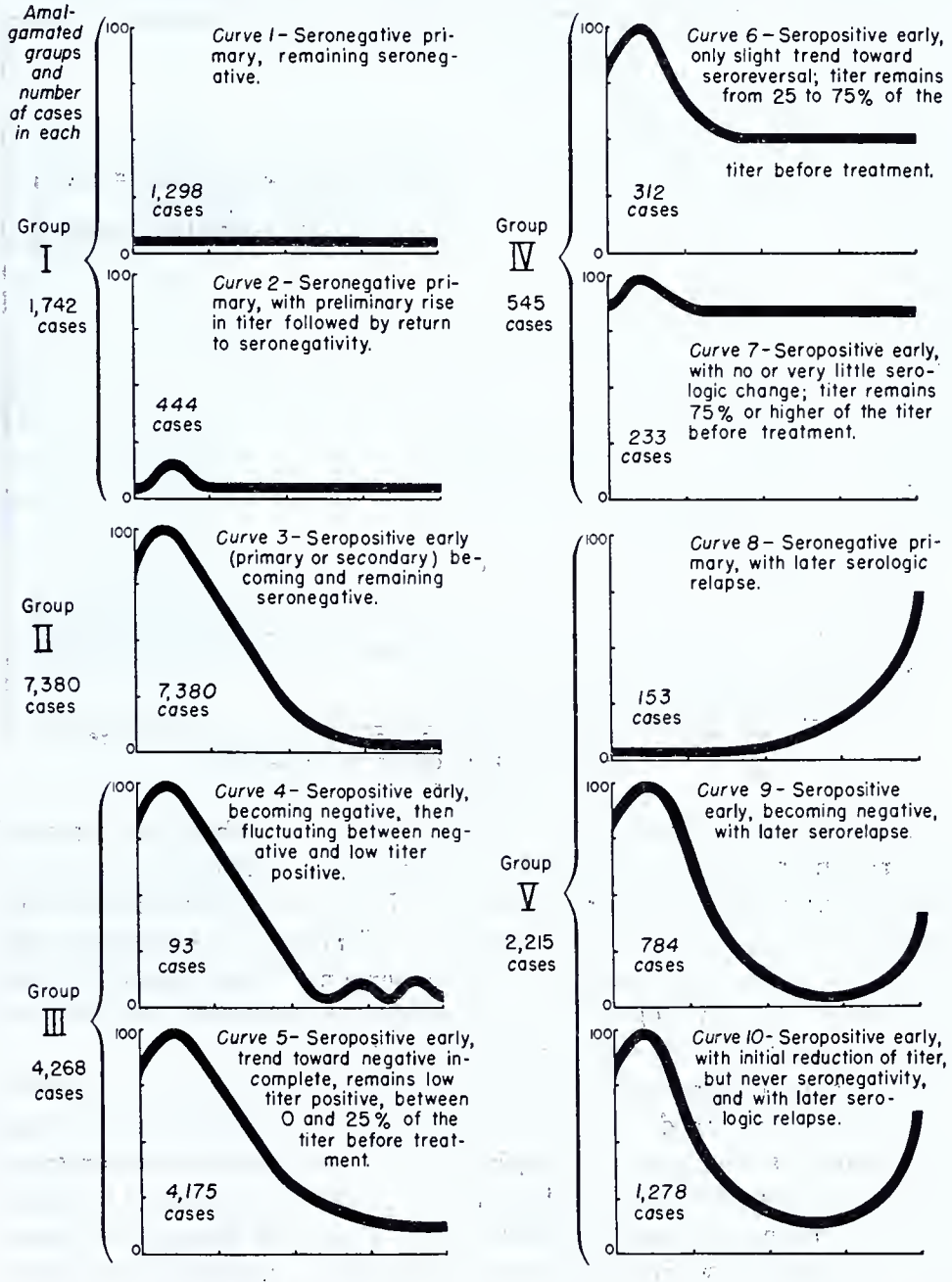
Group III is made up of 4,268 cases of seropositive early syphilis, developing a fall in titer which never reaches confirmed seronegativity; instead, it persists in low titer (25 percent or less of original titer) without showing serorelapse during the first posttreatment year. Group III conforms to curves 4 and 5 of Moore.

Group IV. The 545 cases of group IV are cases of seropositive early syphilis remaining seropositive in high titer.

Group V, comprising 2,215 cases, includes all patients, whether

originally seronegative or seropositive, who developed serologic relapse before the end of the first posttreatment year. Of these, 153 were seronegative primary, with later serologic relapse; 784

Typical Curves of Serologic Response During Ist Post-Treatment Year in Penicillin-Treated Early Syphilis (from Moore)


Amalgamated groups and number of cases in each
Group I
1,742 cases
Curve 1 – Seronegative primary, remaining seronegative.
1,298 cases
Curve 2 – Seronegative primary, with preliminary rise in titer followed by return to seronegativity.
444 cases
Group II
7,380 cases
Curve 3 – Seropositive early (primary or secondary) becoming and remaining seronegative.
7,380 cases
Group III
4,268 cases
Curve 4 – Seropositive early, becoming negative, then fluctuating between negative and low titer positive.
93 cases
Curve 5 – Seropositive early, trend toward negative incomplete, remains low titer positive, between 0 and 25% of the titer before treatment.
4,175 cases
Group IV
545 cases
Curve 6 – Seropositive early, only slight trend toward seroreversal; titer remains from 25 to 75% of the titer before treatment.
312 cases
Curve 7 – Seropositive early, with no or very little serologic change; titer remains 75% or higher of the titer before treatment.
233 cases
Curve 8 – Seronegative primary, with later serologic relapse.
153 cases
Group V
2,215 cases
Curve 9 – Seropositive early, becoming negative, with later serorelapse.
784 cases
Curve 10 – Seropositive early, with initial reduction of titer, but never seronegativity, and with later serologic relapse.
1,278 cases
100
0

The vertical line represents the STS titer. This is arbitrarily shawn in range 0 to 100 to distinguish between high and low titer tests. The horizontal line indicates time after treatment, the length of the line representing ane year. The curves are schematic.

FIGURE 1.

were seropositive early, becoming negative, with later serorelapse; 1,278 were seropositive early, with initial reduction of titer, but never seronegativity, and with later serorelapse.

Several facts of importance at once emerge from an examination of the incidence of clinical failure and the time of its appearance in these five major patterns of serologic response.

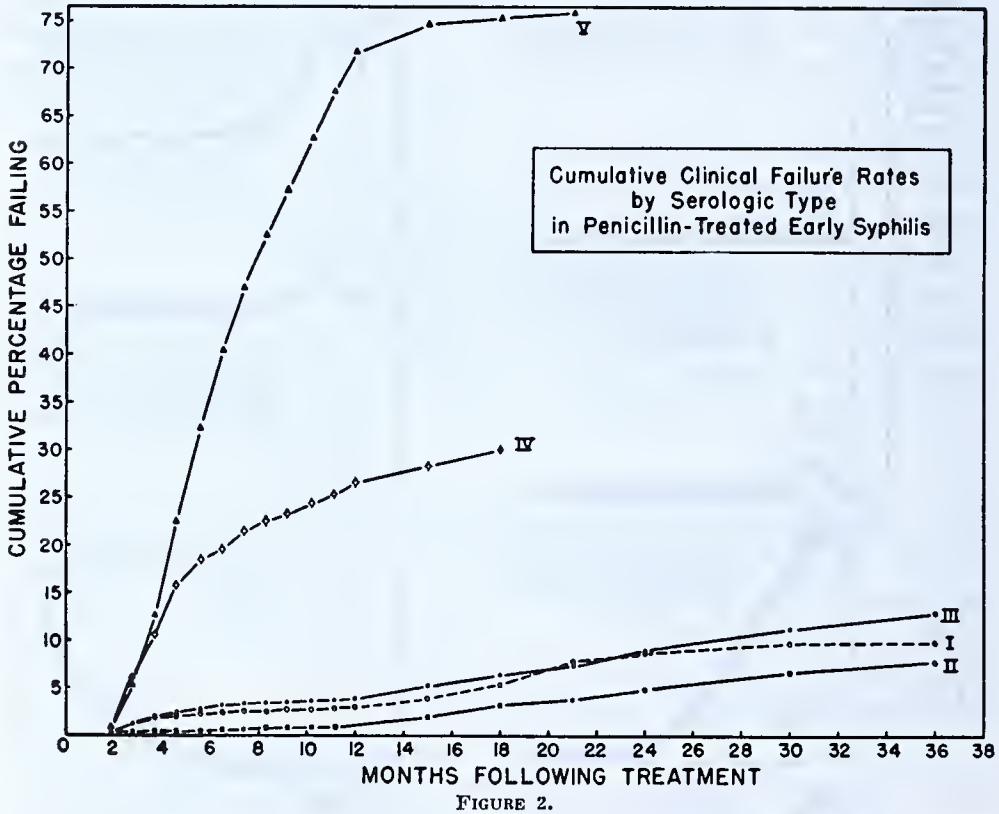


FIGURE 2.

The cumulative rates for clinical failures within the first 36 posttreatment months are very low when the patient remains, or becomes and remains, seronegative. For group I this rate is 9.7 percent; for group II, 7.7 percent. Strikingly, however, this incidence is almost equally low (12.9 percent) when the STS does not become wholly negative, but remains seropositive in low titer during the first posttreatment year (group III).

In marked contrast, by the end of the eighteenth month clinical relapse has occurred in 30 percent of the group IV cases, those who remain seropositive in high titer (as compared with original titer). It is worth noting that in the patients of group IV whose serologic response was practically nil, the total dosages of penicillin employed were not necessarily those usually considered inadequate. More than half of them received more than 1.4 and one quarter more than 3.4 million units.

Finally, serologic relapse occurring in the first posttreatment

year (group V) was followed by clinical relapse in no less than 75 percent of the cases before the eighteenth month after treatment.

More detailed analysis of this experience brings out another fact of possible significance. It suggests that if "confirmed" seronegativity has been attained (groups I and II) or nearly attained (group III) and persists to the first anniversary of treatment, the relatively favorable immediate prognosis assigned to these types is maintained into at least the fourth posttreatment year. On the other hand, cases which have already developed serologic but not yet clinical relapse by the end of the first posttreatment year (group V) probably have a less favorable prognosis than the other groups in spite of a reduction in the incidence of failure in the second year and later as compared to the first year.

Another point of interest was illustrated by these data. If cases still seropositive at the end of the first year but without as yet evidence of serologic relapse (groups III and IV) are examined for the subsequent attainment of seronegativity, it is found that seronegativity may be expected to appear spontaneously in about 40 percent by the end of the second year, and in about 70 percent by the end of the fourth year, without the development of clinical failure at any time.

The data presented have shown a high degree of correlation between serologic response in the first posttreatment year and the probability of clinical failure in persons with early syphilis treated with penicillin.

Our material does contain a number of examples classified as clinical failure appearing during seronegativity, many of them within the second to fourth posttreatment year, and many of them probably reinfections rather than relapses. The existence and perhaps increasing frequency of this occurrence since the introduction of penicillin makes it obligatory that posttreatment observation shall include clinical inspection of the patient as well as quantitative serologic observations. The suggestions which we have as to procedure on the basis of serologic response are therefore not intended to suggest that the physician may omit clinical observations in favor of entire reliance on serologic progress.

With this qualification in mind, our data nevertheless permit certain statements which are of practical importance as to the necessity for re-treatment of penicillin-treated patients with early syphilis who show no signs of clinical relapse, as follows:

1. Whether in seronegative primary or seropositive early syphilis, re-treatment need not be given if the patient remains, or becomes and remains, seronegative.

2. In seropositive early syphilis, re-treatment need not be given because of the persistence of a weakly positive test during the first 12 months after treatment. We are inclined to agree with Thomas that such cases almost certainly do not require re-treatment even if low-titer seropositivity persists for 2, 3, or even more years.

3. On the other hand, if the STS persists for 6 months in high titer, re-treatment should be given at 6 months, regardless of whether clinical relapse has or has not yet appeared.

4. Patients with serologic relapse, of the type illustrated in group V, should in all cases be re-treated as soon as the fact of such relapse is confirmed by a check serologic test.

Five Years of Penicillin Effect Alone on Neurosyphilis[1]

Including Some Comparisons with Prepenicillin Methods

John H. Stokes, Mortimer S. Falk, and George D. Gammon[2]

Section I

The Penicillin-Syphilis Panel at the University of Pennsylvania has adhered to the practice of using penicillin alone in the treatment of neurosyphilis, and presents herewith its report of its fifth year of experience.

The 39 "original inhabitants" have been reduced to 29 by 2 deaths, 4 missing, 1 noncooperative, and 3 delayed reexamina-

---

[1] From the Institute for the Study of Venereal Disease, University of Pennsylvania and the United States Public Health Service cooperating, and the Penicillin-Syphilis Panel of the University Hospital. The Institute, the Departments of Neurology, Ophthalmology, Dermatology and Syphilology, and Pediatrics; the Division of Venereal Disease Control, Philadelphia City Department of Public Health; the Philadelphia General and Pennsylvania Hospitals, and the Children's Hospital are represented in the authorship.

The work described in this paper was done under a grant from the Research Grants Division of the National Institutes of Health, in continuation of a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Pennsylvania.

[2] With the collaboration of Herman Beerman, M.D.; Norman R. Ingraham, Jr., M.D.; William O. La Motte, M.D.; Paul György, M.D.; Elizabeth Kirk Rose, M.D.; John W. Lentz, M.D.; and with the technical assistance of Verna Mayer Stein, Emily Stannard, Jane Barbara Taylor, R.N., and Mildred F. Wills, R.N.

tions. Figure 1 presents the original graph of previous reports, with the results for 1948 represented in the last column. Of 29 re-examined, 22 have achieved normal and near-normal spinal fluids. This represents 59 percent of the total of 37 living patients and 76 percent of the total re-examined whose spinal fluids closely approximate normality after 5 years. Marked improvement in the fluid now stands at 21 percent, the loss over 1947 representing gain in normals and near-normals.

For this year's report figures 2, 3, and 4 of previous reports, giving the detail of behavior in type III spinal fluids which in 1947 had been observed 2 years or more, with curves of best fit, has been replaced by a superposition in a single chart of the curves of best fit carried through 1948, on the same groups of cases. Figure 2 in the present report compares the curves of asymptomatic neurosyphilis, meningovascular neurosyphilis, tabes, and paresis-taboparesis. This represents an addition of the meningovascular data worked up during the past year, to the original charted material.

It will be apparent that the trend toward normality continues but tails off to a very slow descent. Asymptomatic neurosyphilis and tabes show the most tendency to return toward fluid normality, and meningovascular neurosyphilis the least. It seems a fair deduction from this study that once a gradient of improvement is established by penicillin therapy, it tends to be maintained, and to improve very slowly over a period of years, without further treatment.

Table 1 tabulates in cases and percentages the normal, the near-normal and the normal plus near-normal results in the spinal fluids of the various diagnostic categories, comparing 1947 with 1948. The improvement trend is again apparent, and slight but definite in all categories except tabes, which seems to have reached a level at 80 percent normal plus near-normal fluids.

Table 1.—*Central nervous system syphilis observed 2 years or more* [1]

Diagnosis	Total cases		Number of cases of near-normal C.S.F.				Number of cases of normal C.S.F.				Total cases of normal and near-normal C.S.F.			
			1947		1948		1947		1948		1947		1948	
	1947	1948	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Paresis	11	19	3	27	4	21	2	19	6	32	5	46	10	53
Taboparesis	20	27	2	10	6	22	10	50	12	44	12	60	18	66
Tabes dorsalis	55	91	15	27	23	25	29	53	50	55	44	80	73	80
Meningovascular	33	54	5	15	6	11	15	45	30	55	20	60	36	66
Asymptomatic	23	35	7	30	8	23	10	44	20	57	17	74	28	80

[1] 226 cases in 1948.

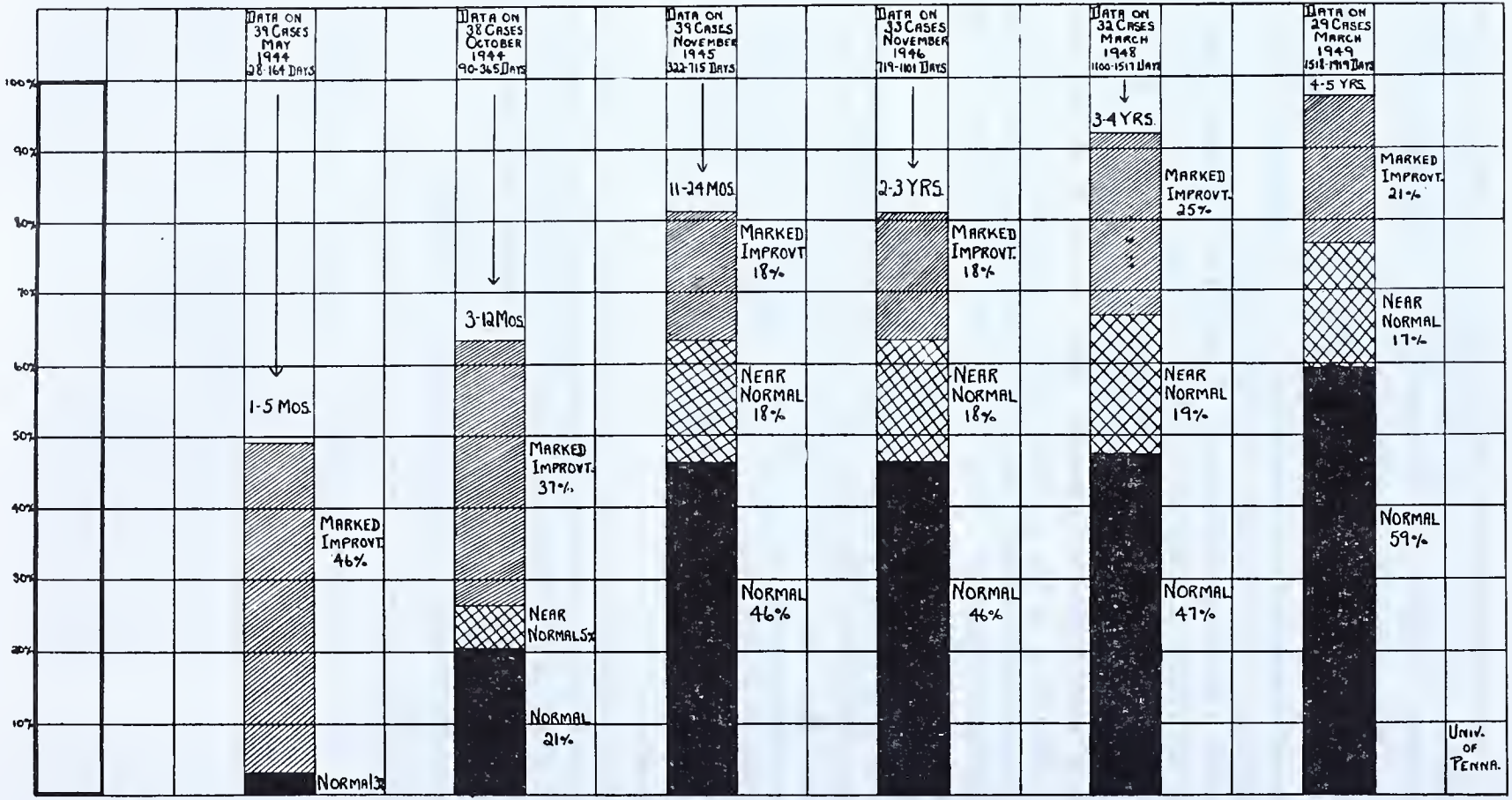


FIGURE 1.—Progress of the original 39 cases of neurosyphilis toward spinal fluid normality, regardless of type of neurosyphilis, dose or number of courses of penicillin.

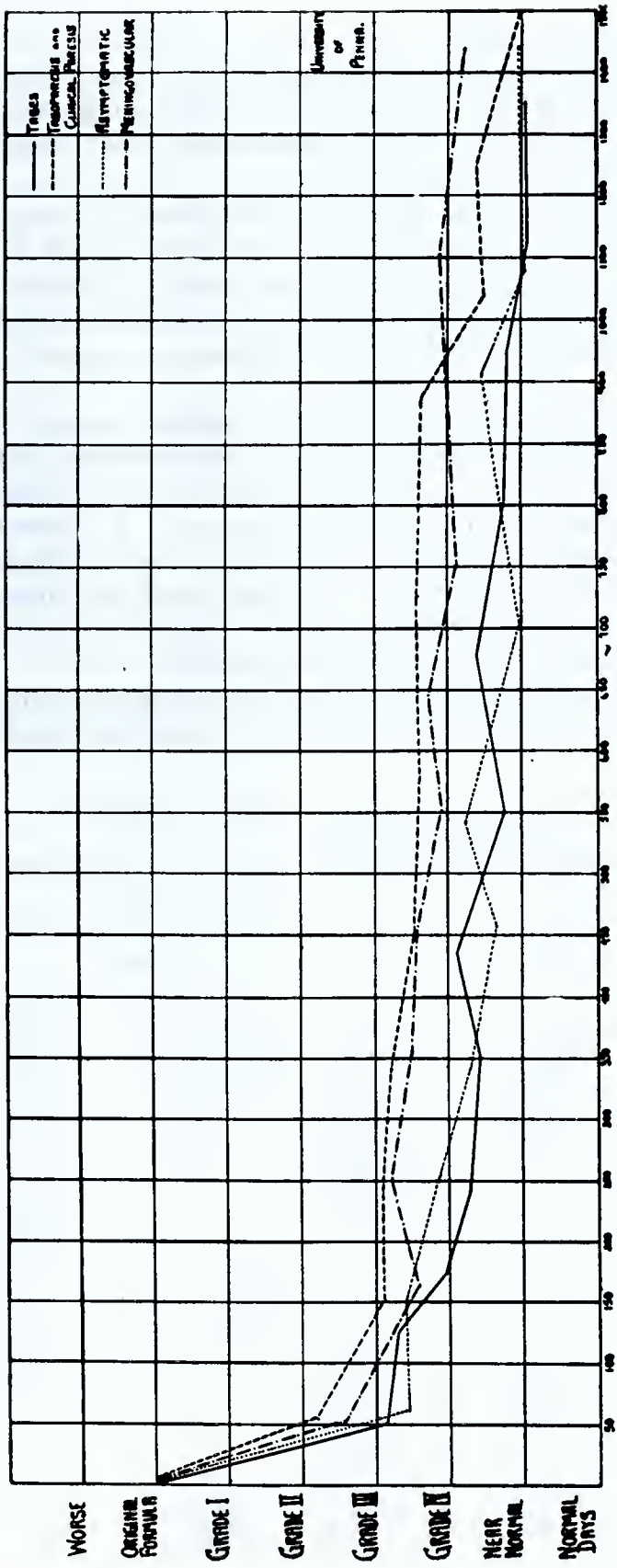


FIGURE 2.—Behavior of the spinal fluid in asymptomatic neurosyphilis, meningovascular neurosyphilis, tabes dorsalis, paresis, and taboparesis.

Progress Indicated by Case Protocols

Tables 2 to 9 inclusive and figure 3 are revised "portraits" made familiar to our audience by previous reports suggesting significant forms of response and long-term results with penicillin alone.

Tables 2 and 3 illustrate lasting results in asymptomatic neurosyphilis, the one with 3.6 million units in two courses and an uninterrupted improvement gradient; the other with 13.6 million units, two courses aggregating 3.6 million units being followed by a third of 10 million units, when signs of relapse appeared in the spinal fluid.

Table 4 represents a patient who, after 8.8 million units in 3 courses, received typhoid vaccine therapy at the four hundred and thirty-eighth day, and was found to have a normal fluid at the one thousand, six hundred and ninety-seventh day; a clinical failure slightly worse than at the start, but with a normal fluid. This illustrates the unpredictability of clinical and the nonconcomitance of clinical and serologic results. Such results as these are obtainable with penicillin without fever.

Table 5 illustrates the apparent conversion of a long-standing Dattner-Thomas inactive fluid to near-normal between the fourth

Table 2.—*Response of asymptomatic neurosyphilis to treatment with penicillin alone*

[No. 8, L. S.; W, F, 41, November 23, 1948. Asymptomatic neurosyphilis. Previous treatment: none. No clinical evidence of CNS syphilis. C.S.F. positive, October 1943.]

Date	Days post penicillin	Kline	Cells	Wassermann	Protein	Mastic	Clinical
			(1) **1,200,000 units penicillin (every 3 hours) 11/27/ to 12/5/43**				
11/27/43	1	64	103	4444	4+	2444411000	
12/14/43	17	8	29	1244	2+	2221100000	
1/12/44	46	32	11	0012	1+	2211000000	
2/9/44	74	32	6	0112	30	1111000000	
3/8/44	102	32	6	0112	40	2211000000	
4/5/44	129	8	4	0011	30	1111000000	
5/5/44	159	32	8	0122	30	2211100000	
5/24/44	178	16	6	0012	30	2221100000	
			(2) **2,400,000 (every 3 hours) 5/28/ to 6/2/44**				
5/28/44	182						Urticarial reaction.
6/2/44	186	4	7	0000	20	1111000000	
10/4/44	310	32	3	0000	30	1110000000	
12/13/44	380	32	3	0000	20	1111000000	
3/7/45	464	8	3	0000	40	1110000000	
6/27/45	576	32	6	0000	20	0000000000	
1/9/46	779	64	2	0000	20	0000000000	
6/19/46	935	32	3	0000	20	0000000000	
1/8/47	1,200	21±0	3	0000	10	0000000000	Asymptomatic.
6/9/48	1.635	2	4	0000	20	0000000000	No change.

and fifth years by a "capping" course of 9.6 million units. It is impossible to predict that such a result will be maintained.

Table 6 represents a negative fluid maintained from the five hundredth day to the one thousand, seven hundredth day after a single course of 1.2 million units of penicillin following an arsenic-heavy-metal and Swift-Ellis failure. The optic atrophy has remained stationary.

Table 7 represents a tabetic who has now remained free of pains and with a negative fluid from the two hundred and twelfth to the one thousand, eight hundred and fortieth day following two courses of 1.2 million units of penicillin.

Table 8 presents a 5-year clinical remission of paresis without serologic recovery under 16 million units of penicillin in three courses.

Table 9 (with table 8) illustrates the importance of clinical control of the laboratory in serologic tests. An overwhelming crop of positive spinal fluid Kolmers on one day led to an in-

Table 3.—*Response of asymptomatic neurosyphilis to treatment with penicillin alone*

[No. 46; J. N.; B, M, 26, February 9, 1944. Asymptomatic neurosyphilis. Previous treatment: 8 arsphenamine, 8 bismuth. No clinical evidence of C. N. S. CSF positive (draft board). Duration of disease, 27 years.]

Date	Days post penicillin	Kline	Cells	Wassermann	Protein	Mastic	Clinical
1/26/44	Pre-penicillin		52	4444	30	4431100000	
		(1) **1,200,000 units penicillin (every 3 hours) 2/9/ to 2/13/44**					
2/9/44	1	2					
2/14/44	6		42	4444	40	2211000000	
3/16/44	29	4	4	0122	30	2332210000	
5/9/44	71	32	RBC	4444	30	4432110000	
6/21/44	127	21±0	16	4444	40	3554221000	
7/18/44	154	Negative	7	4444	20	2333211000	Physical examination negative.
		(2) **2,400,000 (every 3 hours) 8/7/ to 8/15/44**					
8/7/44	174	16					
11/8/44	267	4	8	0011	30	1111100000	
1/3/45	323	4	5	0000	20	1111000000	
4/4/45	415	8	5	0112	20	2221100000	
		(3) **10,000,000 (every 3 hours) 5/18/ to 6/18/45**					
5/18/45	459	16					Physical examination negative.
5/22/45	463	16	4	0012	30	2221100000	
8/1/45	535	1±0	2	0000	10	1110000000	
10/24/45	620	64	2	0000	20	1111000000	
1/23/46	713	16	2	0000	20	1110000000	
5/1/46	812	64	2	0000	20	1110000000	
1/23/47	1,079	4					
5/14/47	1,192	2	0	0000	20	1110000000	Asymptomatic.
5/19/48	**1,560**	**Negative**	**0**	**0000**	**20**	**1111000000**	**Symptomatic.**

vestigation of the source, found to be in a batch of defective complement. Table 9 is worse clinically though improved serologically.

Figure 3 represents the patient who in a period well over 5 years appears to have sustained an arrest of a primary optic atrophy and clinical normality with spinal fluid normality in four courses of penicillin aggregating 16.4 million units. The sector defect in the right visual field, however, needs watching, though the interpretative margin is such that he is regarded as stationary.

Figure 4 shows a 5-year clinical and serologic remission of a typical paresis under 18.4 million units of penicillin in three courses.

This "I had a case" method of presenting penicillin results merely illustrates possibilities, not probabilities. Old-line therapy of varying intensities could show the same case-by-case

Table 4.—*Clinical failure, ultimately normal spinal fluid in clinical paresis*

[No. 7, W. L., B, F, 14, November 27, 1943. Late congenital CNS syphilis, paresis. Previous treatment: 2 arsphenamine and 15 bismuth injections. Personality changes, with impaired intelligence and memory. Irritability, emotional instability, uncertain gait (8 months' duration). Pupils irregular, fixed to light and accommodation. Hutchinsonian teeth. Slurred speech. EEG: suggestive of diffuse disturbance of greater part of cortex.]

Date	Days post penicillin	Kline	Cells	Wassermann	Protein	Mastic	Clinical
9/8/43	Pre-penicillin		12	4444	4+	5555431100	
		(1) **1,200,000 units penicillin (every 3 hours) 11/27/ to 12/5/43**					
11/27/43	1	64	42	4444	4+	5555311000	
2/2/44	64	64	4	1244	2+	4421000000	
		(2) **3,600,000 (every 3 hours) 2/17/ to 2/25/44**					
2/17/44	77	64					
2/25/44	85	32	5	4444	20	5552100000	
4/5/44	127	32	3	2444	40	5555310000	No improvement.
5/17/44	164	32	1	4444	40	5555221100	
10/21/44							Deteriorated—worse.
1/16/45	408	64					
		(3) **4,000,000 (every 3 hours) 1/26/ to 2/15/45**					
2/15/45	438	128					
		Given typhoid, 45 hours at temperature over 103° F.					
3/19/45	470		4	4444	30	4443110000	
7/25/45	598	64	6	0112	10	2221100000	Improved—EEG almost normal Very retarded mentally.
10/25/45	696	256	4	4444	20	5553310000	Seems stationary.
5/1/46	891	256	0	0112	10	2221100000	No great change.
11/20/46	1,088	256	5	4444	10	4443210000	
9/10/47	1,384	256	0	0112	10	2221100000	Mentally W-1.
1/20/48	**1,697**	**256**	**0**	**0000**	**10**	**1111000000**	**Stationary.**

instances. The difference is in the hazards and the protracted miseries of the cure.

Comparison of Spinal Fluid Results with Larger and Smaller Dosages of Penicillin

The range of dosage in individual courses represented in our backlog (table 10) is low in comparison with the high total dosage in repeated courses of 15 to 20 million units, but the results in table 10 are suggestive despite the small numbers of cases. The figures for paresis and taboparesis are too small to be trustworthy. Meningovascular and tabetic neurosyphilis sustain about the same good effect from less as from more penicillin in short or longer observation. Asymptomatic neurosyphilis shows a prolonged ascent in percentage improvement in the low dosage, a rapid ascent and somewhat higher ultimate percentage of improvement in the higher dosage bracket (83 percent normal or near-normal fluids after one year for the higher, 67 percent for the lower levels). Again the figures for all levels are too small.

Aqueous Penicillin versus Penicillin in Oil-Beeswax

This comparison was made on a small amount of material at the dosage level of 4.8 million units. The figures are not statisti-

Table 5.—*Conversion of Dattner-Thomas inactive to negative fluid (?)*

(5 years, 1916 million units)

[No. 22, M.T., B, F., 47, January 4, 1944. Meningovascular syphilis, primary optic atrophy (?). Previous treatment: 53 arsphenamine, 15 tryparsamide, 104 bismuth, and fever (hot-box). History of positive C.S.F. 1940, Argyll-Robertson pupils, hyperreflexia.]

Date	Days post penicillin	Kline	Cells	Wassermann	Protein	Mastic	Clinical
			(1) **1,200,000 units penicillin (every 3 hours) 1/5 to 1/13/44**				
1/5/44	1	4	4	4444	4+	3555210000	
6/14/44	156	Negative	2	4444	30	5555321000	
			(2) **2,400,000 (every 3 hours) 7/17 to 7/26/44**				
9/26/44	229	Negative	3	4444	30	5552100000	No primary optic atrophy
10/10/45	643	Negative	4	4444	20	5555542100	Still some suspicion of P.O.A. (Steele says "No.")
			(3) **6,400,000 (every 3 hours) 11/7 to 11/27/45**				
11/14/45	661	Negative	1	4444	30	4554421000	
7/23/46	930	Negative	1	4444	40	4421100000	No evidence of P.O.A. (La Motte).
6/18/47	1,262	Negative	2	4444	30	4555521000	Some vertigo; pains in legs?
1/14/48	1,470	Negative	2	4444	20	5554321000	Eye and neurol. no change.
			(4) **9,600,000 (every 2 hours) 4/7 to 4/17/48**				
4/7/48	1548	Negative	2	0112	20	2221100000	First day of retreatment.
7/14/48	1,643	Negative	0	4444	30	4555431000	
10/20/48	1,749	Negative	2	1244	30	4444310000	
1/26/49	1,847	Negative	2	0000	30	1111100000	No change.

Table 6.—*Case demonstration of (1) superiority of 1.2 million units penicillin (1943) over Swift-Ellis therapy; (2) rate of C.S.F. response; (3) duration of good effect, C.S.F. normal 2½ years; (4) P.O.A. arrested 3½ years; (5) total observation 6 years, 3¾ years after penicillin*

[No. 12, J. L., W, M, 51, December 14, 1943. Tabes dorsalis with primary optic atrophy. Tendon reflexes absent. OD 6/9, OS light perception. C.S.F. positive December 8, 1941.]

Swift-Ellis 14 treatments + 34 bismuth; CSF examination with each Swift-Ellis, as follows—					Penicillin 1,200,000 units begun 89 days after Swift-Ellis relapse was recognized. CSF findings follow—				
Days	Cells	Protein	Wassermann	Mastic	Days	Cells	Protein	Wassermann	Mastic
1	52	4+	4444	3444210000	1	74	4+	4444	3444210000
8	10	4+	4444	5442211000	43	10	2+	0124	1221000000
15	8	2+	1244	3332210000	85	7	30	0011	1111110000
27	6	1+	0124	2220000000	127	9	30	1122	1222100000
59	16	3+	1244	4442111000	183	10	20	0011	1111100000
75	12	3+	1124	4442210000	287	5	30	0000	1111100000
131	4	Negative	0000	1110000000	413	0	20	0000	1110000000
144	3	Negative	0000	0000000000	501	2	30	0000	0000000000
.....	2	Negative	0000	1110000000	701	RBC	30	0000	0000000000
202	2	35	Positive	1112222000	1,079	3	30	0000	0000000000
216	2	Negative	0000	1110000000	1,359	2	30	0000	0000000000
230	2	+−	0000	1111000000	**1,743**	.....	**20**	**0000**	**0000000000**
250	3	+−	0000	1111000000					
264	4	+−	0011	1111000000					
395	2	Negative	0000	1110000000					
Swift-Ellis stopped, followed by relapse									
583	58	4+	4444	2444310000					
625	51	2+	1244	2443100000					

As much was accomplished by 1,200,000 units of penicillin as by 14 Swift-Ellis and 34 bismuth

Table 7.—*Relief of lightning pains, C.S.F. negative*

[No. 55, N. P., W, M, 38, February 13, 1944. Tabes dorsalis, lightning pains. Previous treatment: 22 arsphenamine, 35 bismuth. Pains (several months). Tendon reflexes absent; pain sense lost in muscles, tendons; anisicoria; slight nystagmus.]

Date	Days post penicillin	Kline	Cells	Wassermann	Protein	Mastic	Clinical (pain)
			(1) **1,200,000 (every 3 hours) 2/23/ to 3/2/44**				
2/23/44....	1	Negative	3	0000	30	1100000000	
3/2/44.....	8	2	3	0000	40	1111100000	
4/5/44.....	42	8	3	0112	40	1111110000	
5/10/44....	77	Negative	RBC	1122	20	2443210000	
6/14/44....	112	1±0	5	0112	30	2222100000	
7/12/44....	140	1±0	2	0000	30	1111100000	
9/13/44....	183	Negative	1	0112	20	2442100000	
			(2) **1,200,000 (every 3 hours) 10/12/ to 10/16/44**				
10/12/44..	212	32	4	0011	20	1111000000	
10/30/44..							Pain gone.
11/22/44..	254	8	1	0112	30	2444311000	Remarkable remission of pain.
3/7/45.....	360	21±0	3	0000	40	1111000000	Marked improvement maintained.
6/26/45....	471	1±0	3	0000	30	1110000000	
11/7/45....	622	1±0	1	0000	40	1110000000	No recurrence.
3/27/46....	767	2	2	0000	40	1111000000	
1/7/47.....	1,050	2	3	0112	40	2221100000	No tabetic pain.
7/16/47....	1,239	21±0	2	0000	50	1111000000	No pain.
1/14/48....	1,415	32	0	0000	40	1110000000	No pain.
3/9/49.....	**1,840**	**doubtful**	**2**	**0000**	**30**	**0000000000**	Has had no pain.

cally significant but are suggestive. All patients were examples of asymptomatic neurosyphilis. Of 31 patients given aqueous penicillin under hospitalization and followed more than 120 days, 18 achieved normal or near-normal spinal fluids (58 percent). Of 36 patients given P.O.B. 600,000 units once a day for 8 days, under hospitalization, 21, or 59 percent, observed for more than 120 days, obtained normal or near-normal spinal fluids. Thus the immediate response of the fluid was almost identical. It remains to be seen whether the ultimate response will show superiority of one over the other.[3] The termination of the neurosyphilis treatment project under the National Institutes of Health has put a stop to the extension of this series.

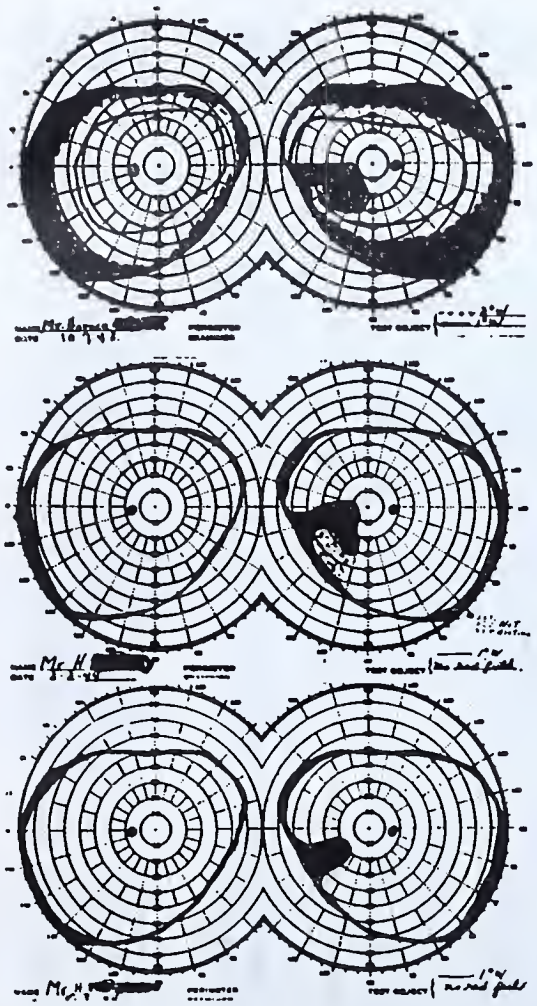
Table 8.—*Five-year clinical improvement in paresis without serologic "cure"; Dattner-Thomas "inactive status"*

[No. 74, H. G., W, M, 43, March 28, 1944. Paresis. Previous treatment: bismuth only. Duration of disease: less than 18 years. Mental deterioration (3 years), progressively worse; delusions of grandeur; emotional lability; euphoria; impotence; dysarthria; shuffling gait; pupils sluggish; hyperesthesia of soles.]

Date	Days post penicillin	Kline	Cells	Wassermann	Protein	Mastie	Clinical
	Pre-penicillin	64	62	4444	100	5555555431	Clear
			(1) **4 million units penicillin (every 3 hours) 3/28 to 4/13/44**				
4/23/44....	27	32	4	4444	50	5555543210	
11/2/44....	217	32	?	4444	30	4555542111	
3/21/45....	356	4	4	4444	30	5555542110	Definite improvement.
			(2) **2,400,000 (every 3 hours) 4/3 to 4/11/45**				
5/16/45....	412	Negative	5	4444	40	4555542110	
10/31/45..	582	64	3	4444	20	4555332100	Symptomatic improvement.
10/23/46..	947	16	3	4444	40	3554211000	Improvement maintained.
			(3) **9,600,000 (every 2 hours) 11/13 to 11/23/46**				
11/20/46..	976	.....	1	4444	30	4555431000	Improvement: General B-4, euphoria B-1, mental B-3.
9/10/47....	1,258	32	0	4444	40	2455441000	(1) Greatly improved. (2) Wife says no better.
12/31/47..	1,374	4	1	1244	30	2344420000	Improvement maintained (Churchill)
12/15/48..	1,723	doubtful	0	Positive [1] 4+	30	2444210000	Improvement maintained; works; marked euphoria; little sensorial damage. (Wife now thinks better than prepenicillin).

[1] False positive day in laboratory traced to defective complement.

[3] Gammon, in an unpublished study in April 1948, surveyed the small amount of material treated with P.O.B. to that date and concluded that the asymptomatic group showed a lower rate of normality and more cases in which a high cell count suggested a continuing infection which required retreatment. Several cases on P.O.B. in his opinion developed signs of neurosyphilis, thereby becoming symptomatic cases.

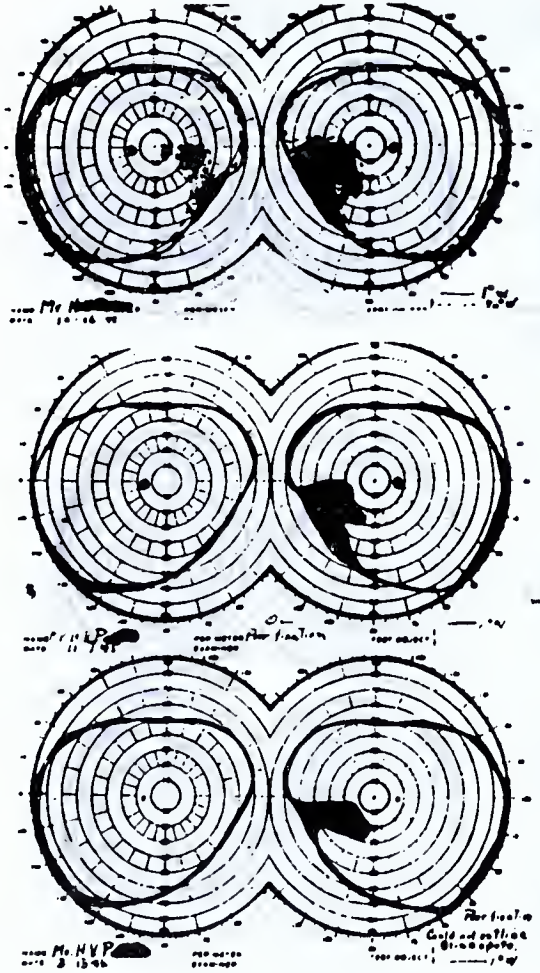


No. 3 H.P. W.M. 38 11/17/43.
Previous treatment: routine 18 months 1937-38.

Episode of blurred vision and diplopia in 1937, which cleared under routine therapy. Visual loss recurred 9 months before admission. Pupils irregular and sluggish. Visual fields contracted; tendon reflexes absent; euphoria, irritability.

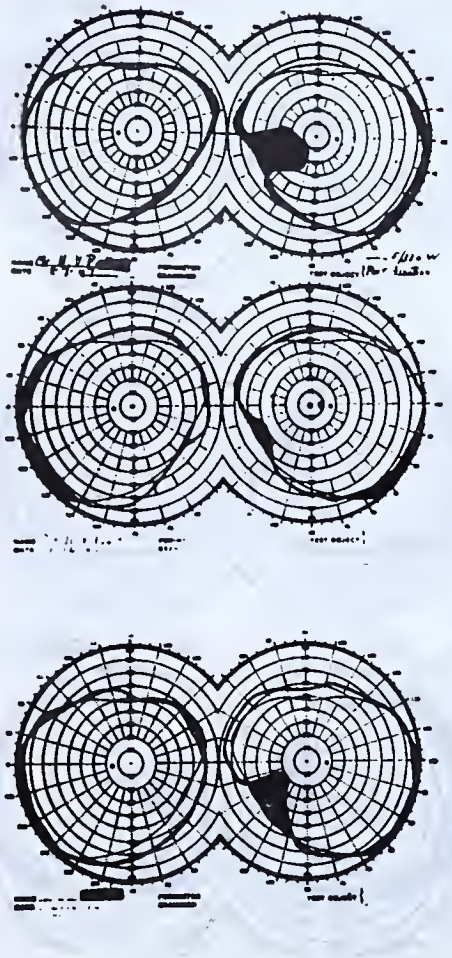
PREPENICILLIN FIELDS

Date	Days post-pen.	Kline	Cells	Wassermann	Protein	Mastic
11/ 3/43	Pre-pen.		72	4444	4+	4432210000
1,200,000 units penicillin (every 3 hours) 11/18 - 11/26/43						
11/18/43	1	16				
11/19/43	2		29	0123	3+	4432210000
12/ 1/43	13	8	12	0012	2+	2211000000
12/21/43	41	2	23	0122	2+	2211000000
2/ 2/44	76	2	10	0112	1+	3211000000
1,200,000 (every 3 hours) 2/20 - 2/28/44						
3/ 1/44	104	16	11	0112	20	2211100000
3/29/44	132	2	5	0012	20	1111100000
5/ 3/44	164	1±0	5	0012	20	2211000000



7/26/44	250	2	2	0000	20	1110000000
4,000,000 (every 3 hours) 10/2 - 10/16/44						
10/ 2/44	313	Neg.	4	0112	10	3332100000
10/16/44			3	0012	10	2221100000
11/29/44	376	4	8	0112	20	2221100000
2/28/45	469	21±0	6	0112	20	2222110000
10,000,000 (every 3 hours) 5/6 - 5/21/45						
5/ 6/45	536	Neg.	1	0011	20	1111100000
5/31/45	561		3	0000	20	1111000000
11/ 7/45	719	21±0	3	0000	10	1100000000
3/13/46	846	Neg.	3	0000	20	1100000000

FIGURE 3.—Taboparesis with primary optic atrophy.



Date	Days post-pen.	Kline	Cells	Wasser-mann	Pro-tein	Mastic
5/ 7/47	1267	21±0	8	0000	20	1111000000
9/17/47	1398		1	0000	10	1111000000
2/16/49	1916	Neg.	2	0000	10	1110000000

This patient has lost all clinical evidence of cerebral impairment and is his normal self personally and occupationally. Has withstood streptomycin and collapse therapy for pulmonary TB (?). The ophthalmologist rates him as unchanged.

FIGURE 3 continued.—Taboparesis with primary optic atrophy.

Table 9.—*Clinical progression, in spite of penicillin*

[No. 45, A. K., W, M, age (?), February 7, 1944. Taboparesis. Previous treatment: 30 arsphenamine, 50 bismuth. Routine STS positive 1942. Positive C.S.F. January 3, 1944. Anisicoria, coarse tremor of tongue. Mental: station, gait, and reflexes O. K.]

Date	Days post penicillin	Kline	Cells	Wassermann	Protein	Mastic	Clinical
1/3/44	Pre-penicillin	.....	1	0122	2+	1233310000	Clear
			(1) **1,200,000 units penicillin (every 3 hours) 2/7/ to 2/11/44**				
2/7/44	1	8					
2/23/44	18	1±0	5	4444	20	2444111000	
3/29/44	45	32	3	0122	20	1221000000	
5/3/44	80	2	RBC	0124	20	2443210000	Tremor of tongue and anisicoria; otherwise negative.
10/3/44	233	21±0	4	0012	20	2221100000	Slight ataxia; impression: no change(?).
1/30/45	352	16	0	0112	20	2221100000	
			(2) **2,400,000 (every 3 hours) 5/4/ to 5/11/45**				
5/4/45	447	21±0	.....	.....	.....	.....	Somewhat unstable; has roaring in head.
5/8/45	451	.....	3	0012	20	2221100000	
6/12/45	486	32	3	0000	10	0000000000	
11/5/45	636	Negative	3	0000	20	1110000000	Continues to have roaring in head. Romberg sl. positive.
2/27/46	750	21±0	3	0000	20	1110000000	Has had some hallucinations. Impression: paresis worse.
			(3) **6,400,000 (every 3 hours) 3/29/ to 4/8/46**				
3/29/46	781	32					
4/3/46	786	.....	4	0000	20	1110000000	
1/22/47	1,085	Negative	3	0112	20	1222100000	Some pain in right calf; still has roaring in head.
9/3/47	1,304	4	4	1244	20	2344210000	No change (?).
2/25/48	1,479	Negative	2	0000	20	0000000000	No clinical change.
12/15/48	**1,772**	**2**	**0**	**Positive 4+** [1]	**20**	**1110000000**	

[1] False positive day in laboratory traced to defective complement.

Section II

The second section of this report attempts a beginning of an on-the-spot comparison, from University Clinic records, of the outcome of treatment of neurosyphilis with arsenicals, both trivalent and pentavalent, heavy metal, and fever (usually typhoid vaccine) with those reported for penicillin. Great difficulties and a late beginning of this attempt at a comparative backlog make the study more than incomplete but some of the findings are suggestive and a help in interpreting the intrinsic accomplishment of penicillin. For the collection of such material the records of even a couple of decades and a reasonably good clinic proved a poor field. The follow-up or recheck examination was inadequate,

Table 10.—*Comparison of spinal fluid results in large and small dosage*

	Type of Neurosyphilis	9.6 G in one course			Less than 4.8 in one course		
		Total Cases	Normal or near normal	Percent normal or near normal	Total cases	Normal or near normal	Percent normal or near normal
Followed more than 120 days.	Paresis	13	4	31	10	2	20
	Taboparesis	12	3	25	14	4	29
	Meningovascular	29	15	52	33	17	52
	Tabes dorsalis	35	15	43	35	17	49
	Asymptomatic	7	5	71	20	6	30
Followed more than 365 days.	Paresis	8	2	25	3	2	66⅔
	Taboparesis	6	1	17	5	4	80
	Meningovascular	13	9	69	15	13	87
	Tabes dorsalis	22	11	50	10	5	50
	Asymptomatic	6	5	83	6	4	67

so that of a material observed two years or more, 50 percent was unusable from the record standpoint, and additional discards were necessitated by throwing out tabes which was seronegative to start with. Only a sampling was begun (every third record pulled), and all with less than 2 years' follow-up were discarded. There are available at this time 51 records chosen on the basis of adequate spinal fluid data and two or more years of observation, which we hope represent only the beginning of the possible numerical yield from this file material in the coming year. Of these 51 cases the following statements may be made.

Histories were included solely on the basis of length of observation and the adequacy of spinal fluid reports. Of the total, 11 were asymptomatic neurosyphilis, 11 were meningovascular, 20 were tabetic, 5 paretic, and 4 taboparetic. The observation period ranged from 2 to 5 years in 24; 6 to 9 years in 15; 10 to 13 years in 7; and 14 to 20 years in 5 cases. The initial spinal fluid was type I in 2 cases, type II in 10 cases, and type III in 39 cases (76 percent). The large preponderance of resistant spinal fluids is apparent, which provides a stiff test for treatment.

No. 70 H.M., W.F.47 3/23/44
CNS syphilis, taboparesis
Previous treatment: none

Progressive gait changes (2 years); personality and mental changes (6 months); delusions, garruloue, speech slurred. Unable to walk; gross tremors, disoriented, schilles and patellar reflexes absent; anisicoria; EEG inconclusive. Total observation 1262 days.

Date	Days post-pen.	Kline	Cells	Wasser-mann	Pro-tein	Mastic	Clinical
3/17/44	Pre-pen.			4444	47	4432210000	Patient could not write or do housework. Had auditory hallucinations, personality changes, disorientation, tremor of tongue, hands and mouth, slurred speech. On second day of penicillin therapy, had Herxheimer reaction with right-sided convulsions becoming generalized. After 24 hours, penicillin was reinstituted at half-dose, to total 1.2 million units, without untoward effect. By 16th day, completely oriented; memory, speech, tremor improved; EEG improved. In 4 months patient tremor-free, speech and writing normal, well oriented, hallucination-free, and satisfactorily performing housework, including marketing with points and driving car.
(1)	4,000,000 units penicillin (every 3 hours) 3/23 to 4/6/44						
3/23/44 3/30/44	1	64					
4/18/44 5/13/44	26	64	6	4444	20	4443310000	
6/ 1/44	70	64	12	4444	20	5553211000	
7/11/44	110	64	1	0012	30	2221100000	
9/26/44	187	64	3	0112	20	2221000000	
10/ 6/44							
4/17/45	392	128	1	0112	20	2221100000	
(2)	4,800,000 (every 3 houre) 9/17/ to 10/2/45						
12/18/46	1008	64	3	0012	20	2221100000	
2/ 6/47	1057	128	?	0000	10	0000000000	
(3)	9,600,000 (every 2 hours) 2/7/ to 2/17/47						
9/ 3/47	1262	128	1	0000	30	1100000000	This patient seen 8 times since 10/6/44 and treated with 13.4 million units additional penicillin (3 courses). Has a normal fluid (13 months) and rates a grade 3 to 4 clinical improvement, maintained.
3/ 3/48	1435	128	2	0000	20	0000000000	
2/23/49	1797		2	0000	20	0000000000	Improvement maintained; perhaps slightly euphoric.

Sept 3 1947 Dr Jammoni
Helen L. Marioni
Feeling very well

3/23/49

Hospl
Hospital of University of Penn.
Bethlehem Presbytar Church
Broad & Diamond St
Phila Pa

FIGURE 4.—A good result, clinical and serologic, in paresis.

Treatment was a mixture ranging from as little as four arsenical and eight bismuth injections alone, to extended treatment with arsenical, heavy metal, tryparsamide, and fever. In 3 cases, small amounts of intraspinal Swift-Ellis therapy were rated as negligible. Of the 51 patients, 11 had received trivalent arsenical and bismuth, 21 had received tryparsamide, and 19 fever (typhoid vaccine), in various proportions and combinations.

Taken in the aggregate, 32 of the spinal fluids, or 63 percent, became normal or near-normal and stayed so without relapse within the period of observation. Nine became normal or near-normal after relapse (17 percent). Thus, a total of 41, or 80 percent, achieved normal or near-normal fluids in from 2 to 20 years of observation under a wide range of prepenicillin treatment, excluding malaria, hypertherm, and Swift-Ellis intraspinal, but including typhoid vaccine pyrexial therapy.

Though the break-down includes too small figures and too many interpretative loopholes, it is interesting that of 11 patients receiving preponderantly arsenical and bismuth, 73 percent secured normal or near-normal fluids; of 19 patients receiving

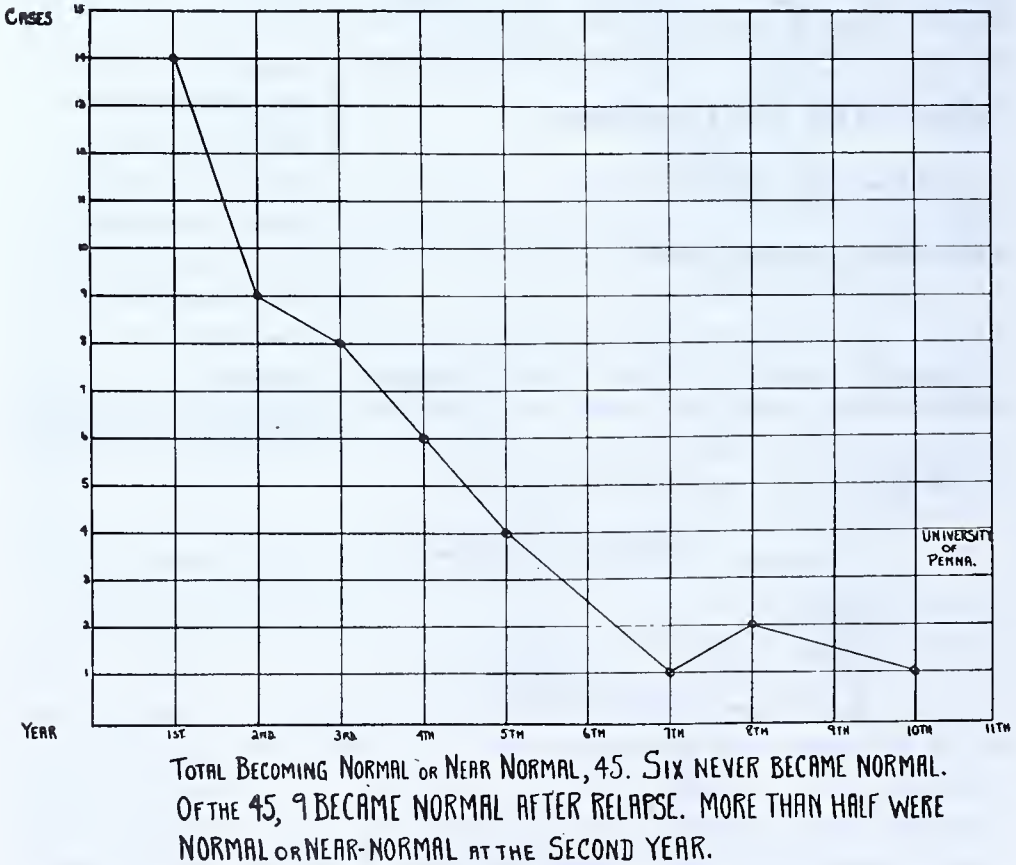


FIGURE 5.—Prepenicillin therapy of 51 cases of neurosyphilis, showing year in which first normal or near-normal spinal fluid was identified, after treatment was begun.

fever, 69 percent (probably loaded by cases showing unfavorable progress under other methods) became normal or near-normal, and of the 21 patients receiving tryparsamide, 95 percent achieved normal or near-normal fluids. Tryparsamide, during this period, was as much a "desperation" measure as fever.

Taken by diagnostic category, of 5 paretics, none became normal in the fluid; of 4 taboparetics, 2 became normal; of 20 tabetics, 12 became normal; of 11 meningovascular cases, 6; and of 11 asymptomatics, 8 became normal. (This is strict normal, not near-normal.)

Figure 5 represents with reservations a curve or gradient of decline of spinal fluid abnormality in the 45 patients whose fluids became normal or near normal, under prepenicillin therapy. Spinal fluids in this material were often examined irregularly and sometimes at long intervals so that the decline of abnormality might well have been somewhat more abrupt, and more like that of figure 2, had examinations been at 90- to 120-day intervals; though it is hardly to be expected that it would equal that of penicillin.

The type of prepenicillin treatment producing a decline to normal or near-normal fluid within 2 years (23 cases) was as follows: only 4 received fever; 8 were treated with trivalent arsenical; and 11 received tryparsamide.

Case Protocols on Prepenicillin Therapy

This material, in individual cases, contains some reminders of importance to penicillin therapists. Table 11 recalls, though the observation period is too short to cover relapse possibilities, the often forgotten fact, how little of the old-line treatment, and by inference, any modern treatment, does how much! Working without spinal fluid controls and follow-up, the physician now seems inclined to pile Ossa on Pelion with scores of 30 million units of penicillin when 10 million or less would have done the work. Table 12 shows again how little did how much—but with spinal fluid relapse, only picked up in the sixth year; and yet with a 10-year history of neurosyphilis without a symptom, a normal fluid was obtained after the twelfth year by tryparsamide and bismuth. Table 13 shows a relapser, relapsing cutaneously and in the nervous system after 31 arsenical and 61 bismuth injections; obtaining a normal fluid in a year on 24 tryparsamide and 65 bismuth injections; and holding it for 11 years. Table 13 shows a trivalent-arsenical-bismuth-fever result with a normal fluid maintained 8 years. Table 14 shows the seesaw fluid, relapse or laboratory error (?) which in various degrees of fluctuation is beginning to annoy penicillin workers today.

Table 11.—*Prepenicillin therapy group, 1948–1949, University of Pennsylvania*

[Heavy metal, trivalent arsenical, tryparsamide, fever]

No. 9438. Initials: M.A. Diagnosis: Meningovascular neurosyphilis. 12 years' observation (1928–40)

Year	STS	C.S.F.					Remarks
		Date	Cell	Wassermann	Protein	Mastic	
1928	44	11/3/28	53	4444	3+	4555421100	Severe headaches—pupils fixed to light; decreased pain sense.
Treatment: 63 Bi; 4 Bismarsen; 12 As; 3 Tryp.							Headaches disappeared. Rest, then lapsed.
7-Year lapse from treatment							
1935	Neg.	2/13/35	0	0000	0	1100000000	Rest.
1940	Neg.	Not done					No clinical progression.

No. 18467. Initials: S.M. Diagnosis: Meningovascular neurosyphilis. 2 years' observation (1933–35)

1933	44	5/5/33	28	4444	4+	5432110000	Argyll Robertson pupils; otherwise clinically negative for syphilis.
Treatment: 8 Bi; 4 As							Lapsed—interval 1½ years.
1935	44	3/18/35	2	0000	0	1110000000	No clinical progression.

How little treatment may lead to arrest!
HOW LITTLE DOES HOW MUCH!

Discussion

With apologies for the deficiencies of our pilot study of prepenicillin therapy of neurosyphilis (recalling also that it does not include malaria) one is impressed by the effectiveness of old-line treatment, and particularly tryparsamide. The chief gains seem to have been so far in the rapidity, ease and safety with which results are secured by penicillin. Penicillin results seem, too, to be durable and of much the same order of magnitude as those suggested by the pilot study of prepenicillin treatment. Attention is directed to the gradients of improvement suggested in figures 2 and 5. These certainly seem to support the belief that time is of the essence in achieving and interpreting spinal fluid and clinical results in neurosyphilis. What is needed most of all is a study, impractical though it may be, of the gradient of spontaneous recovery in the spinal fluids of *untreated* patients over a long period of years. There is much reason to believe that the tendency to "burn out" is an important element in favorable prognosis; that

what treatment does, whether much or little, is to give a push that initiates and accelerates a process already in existence; that it is the inadequacy of this protective or defensive reaction that in the end determines the outcome, rather than some brash and lightning-like miracle of direct spirochetostatic or spirillicidal reaction of drug or antibiotic with organism. The patient who cannot "use"

Table 12.—*Prepenicillin therapy group, 1948–1949, University of Pennsylvania*

[Heavy metal, trivalent arsenical, tryparsamide, fever]

No. 7506. Initials: J.J. Diagnosis: Early asymptomatic CNS syphilis, (about 1 year's duration). 15 years' observation (1927–41)

Year	STS	C.S.F.					Remarks
		Date	Cell	Wassermann	Protein	Mastic	
1927	44	12/31/27	N.D.	0023	0	3210000000	Asymptomatic CNS syphilis.
Treatment: 3 Bi; 8 As; 47 Bismarsen.							
1931	Neg.	4/10/31	1	0000	0	1100000000	
Lapsed 6 Years							
1937	44	11/12/37	38	4444	4+	3555543100	No clinical evidence of CNS involvement. Possibly CV syphilitic aortitis.
Treatment: 15 Bi; 30 Tryparsamide.							10 years of neurosyphilis without symptoms.
1938	44	9/23/38	2	0011	±	1111000000	
Treatment: 10 Bi; 23 Tryparsamide.							
1939	44	5/19/39	2	0000	16 mg.	1110000000	Neg. CSF established in twelfth year, after relapse and tryparsamide-bismuth.
Treatment: 7 Bi; 13 Tryparsamide.							Rest.
1941	44	11/11/41	1	0000	0	1110000000	No clinical progression.

treatment; the patient who has sustained irreparable damage before treatment begins, and the patient who suffers a progressive functional or structural scarring effect following treatment; these are the ones who succumb, and make up the toll of poor results and failures. Four arsenical and six bismuth injections, or 1.2 million units of penicillin, may on occasion be equally effective, shall we say, in initiating the curative gradient in the lucky individual. No amount of anything can do it in the fatally unlucky or the already badly damaged patient.

Table 13.—*Prepenicillin therapy group, 1948–1949, University of Pennsylvania*

[Heavy metal, trivalent arsenical, tryparsamide, fever]

No. 16829. Initials: W.B. Diagnosis: Secondary and recurrent late cutaneous syphilis: asymptomatic neurorecurrence, Type III. 14 years' observation (1932–46)

Year	STS	C.S.F.					Remarks
		Date	Cell	Wassermann	Protein	Mastic	
1932	44	5/19/32	Not done				Early secondary syphilis 5/19/32.
Treatment: 20 Bi; 15 As.							
1932	Neg.	9/16/32	1	0000	0	1100000000	
Treatment: 41 Bi; 16 As.							Treatment for secondary syphilis 31 As, 61 Bi. Rest; then lapsed; interval 2 years.
1934	44	12/12/34	48	4444	4+	5444211000	No clinical evidence of CNS syphilis. Late cutaneous syphilis—noduloulcerative recurrence.
Treatment: 65 Bi; 24 Tryparsamide.							
1935	Neg.	11/1/35	1	0000	0	1110000000	Neg. CSF established in 11 months; 24 Tryp. and 65 Bi.
Treatment: 35 Bi.							Rest.
1938	Neg.	2/18/38	1	0000	0	1111100000	
							Rest.
1943	Neg.	3/3/43	0	0000	0	1111000000	
							Rest.
1946	Neg.	2/20/46	0	0000	30 mg.	0000000000	Sluggish pupils—hypoactive patellars. Normal fluid 11 years.

Neurorecurrence—a tryparsamide result.

Summary

1. The improvement figures on the spinal fluid (normal or near-normal) previously attained have been held or slightly improved in 1948, and range from 53 percent in paresis to 80 percent in tabes, and in asymptomatic neurosyphilis.

2. Meningovascular neurosyphilis shows slightly poorer long-term spinal fluid results than any other type (fig. 2).

3. Case protocols representing a variety of results are brought up to date (tables 2 to 11 and figs. 3 and 4).

4. Re-treatment of relapse or slow response with larger total doses (approximating 10 million units in 2 hours, round-the-clock hospitalization sessions at 80,000 to 100,000 units per injection of crystalline penicillin G) is indicated.

5. Totals of 18 million units have been used.

6. Lasting results may follow much smaller dosage.

7. In any phase of neurosyphilis including paresis, there is hope for arrest by penicillin up to 5 years' observation.

8. Serologic cures without clinical improvement, and the reverse, may be obtained.

9. The Dattner-Thomas fluid type of long standing may respond (perhaps only temporarily) under repeated penicillin therapy.

10. Improvement and 5-year arrest of progressive and relapsing primary optic atrophy in taboparesis, with prolonged fluid normality is a possibility by repeated courses of penicillin alone.

11. Tabetic pain may occasionally be given prolonged relief by penicillin even in small total dosage, and always deserves a trial.

Table 14.—*Prepenicillin therapy group, 1948–1949, University of Pennsylvania*

[Heavy metal, trivalent arsenical, tryparsamide, fever]

No. 21342. Initials: V.A. Diagnosis: Tabes dorsalis. 11 years' observation (1935–46)

Year	STS	C.S.F.					Remarks
		Date	Cell	Wassermann	Protein	Mastic	
1935	44	4/10/35	24	4444	4+	5555421100	Gait changes; poor coordination; positive Romberg.
Treatment: 35 Bi; 18 As.							
1936	44	3/13/36	12	4444	4+	5553210000	
Treatment: 4 As—Fever (typhoid vaccine)							
1936	44	5/8/36	5	2344	3+	4442111000	
Treatment: 23 Bi; 11 As.							
1937	Neg.	1/15/37	4	0011	1+	1222100000	
Treatment: 25 Bi; 18 As.							
1938	Neg.	3/18/38	4	0000	1+	1111110000	Neg. CSF established in 3 years. Total treatment: 83 Bi, 51 As, Fever.
Treatment: 17 Bi.							
1940	Neg.	2/2/40	0	0000	0	1100000000	
Treatment: 23 Bi.							
1941	Neg.	5/23/41	3	0000	0	1111000000	
Treatment: 8 Bi.							Lapse 5 years.
1946	Neg.	5/14/46	0	0000	30 mg.	1111000000	Neg. CSF maintained 8 years. No clinical progression.

An arsenical, heavy metal, fever result.

12. In a small series of cases comparing higher total dosage (9.6 million units) with lower total dosage (less than 4.8 million units) the higher seems to have some slight but not statistically established advantage. Though we have adopted 9 million units as our starting dosage, we do not feel that the superiority of high dosage is proved by our experience.

13. A comparison of round-the-clock aqueous penicillin G with penicillin in oil-beeswax at 600,000 units once daily, in a small series of asymptomatic neurosyphilitics (66 cases) at a total dosage level of 4.8 million units, showed practically no difference in fluid response in 120 days. If borne out for other retarder-penicillin combinations and longer observation, this would justify ambulatory treatment at least of asymptomatic neurosyphilis.

Table 15.—*Prepenicillin therapy group, 1948–1949, University of Pennsylvania*

[Heavy metal, trivalent arsenical, tryparsamide, fever]

No. 18804. Initials: M.H. Diagnosis: Taboparesis. 10 years' observation (1933–1943)

Year	STS	C.S.F.					Remarks
		Date	Cell	Wassermann	Protein	Mastic	
1933	Neg.	6/30/33	8	1244	3+	4543110000	Gait changes. Sluggish pupils. Tongue tremors. Dysarthria.
Treatment: 60 Bi; 60 Tryparsamide.							
1935	Neg.	4/17/35	5	0000	0	1110000000	
Treatment: 15 Bi; 30 Tryparsamide.							
1936	Neg.	10/2/36	6	4444	4+	4555555320	90 Tryp; 75 Bi. to date.
		11/20/36	7	0000	±	1111111000	"See-saw fluid" laboratory or physiologic variation.
Treatment: 20 Bi; 50 Tryparsamide.							
1938	Neg.	2/11/38	2	0011	1+	2331100000	
Treatment: 2 Bi; 30 Tryparsamide.							
1938	Neg.	11/11/38	RBC	0000	0	1110000000	Neg. CSF established at 170 Tryp, 97 Bi. in 5th year.
1939	Neg.	5/12/39	2	0000	0	1110000000	
Treatment: 25 Bi; 12 Tryparsamide.							
1941	Neg.	9/30/41	2	0000	?	1110000000	
Treatment: 12 Bi.							
1943	Neg.	9/22/43	2	0000	0	1110000000	No clinical progression. Negative CSF, no progression 5 years. Total treatment 192 Tryp, 134 Bi.

14. A small pilot study of prepenicillin therapy of neurosyphilis (51 cases) is reviewed as background for interpreting penicillin effects. This study, to be continued into the coming year, suggests that absurdly little treatment with arsphenamine and bismuth alone may be effective; that without malaria but with tryparsamide and typhoid vaccine (and notably the former) normal and near-normal fluids were obtained in 80 percent of the patients in an observation period of 2 to 20 years.

15. In this pilot study, more than half the cases which achieved a normal or near-normal fluid did so by the second year (see fig. 5); 9 of 45 became normal later after relapse, through prolongation and intensification of treatment; only 6 of 51 cases failed to become normal or near-normal within the 2-to-20-year period. The scattering of types of neurosyphilis through the diagnostic categories and the results by category though statistically not significant, resembled those in the penicillin study.

16. It is suggested that penicillin, like the older therapies, tips a balance between patient defense and disease offense; that the amount of treatment needed to accomplish this is not clearly predictable, even by the spinal fluid type. It varies from individual to individual and requires rigorous and prolonged observational control, including repeated spinal fluid examination for its estimation and the determination of course and outcome, under penicillin as under the older methods.

Penicillin Treatment of Late Neurosyphilis—One- to Five-Year Follow-Up with Special Reference to Clinical Failures[1]

David Landau, Israel Kopp, Augustus S. Rose, and Harry C. Solomon

During the past 5 years several reports from the Boston Psychopathic Hospital have been made, giving the results of the investigations of penicillin treatment in neurosyphilis. Although governed by caution engendered by previous experience in the treatment of this disease, we were impressed by the success of penicillin treatment, and accordingly placed emphasis on the evidences of success. The most outstanding evidence of the effectiveness of treatment with penicillin is to be found in a study of the changes in cerebrospinal fluid. Clinical factors are more difficult to evaluate, but they too, in a large series, show strikingly good results.

In the 5-year period from February 1944 to February 1949, we have treated a total of 446 patients (table 1). Of these, 52 (12 percent) are dead, 17 (4 percent) are lost, and 377 (84 percent) remain in our follow-up series.

Table 1.—*Status of 446 neurosyphilis patients treated with penicillin between February 1944 and February 1949*

Status	Number	Percent
Dead	52	12
Lost	17	4
Under follow-up	377	84
Total	446	100

Of the 52 deaths occurring in this series, 33, or 64 percent, died within the first year of treatment. Of this group, general paresis is considered to be a contributing factor in 16 cases. The adjusted mortality rate is 4 percent.

Material and Methods of Treatment

Patients were treated with penicillin alone or in combination with fever therapy. From February 1944 to June 1945, penicillin was given intramuscularly in dosages of 3 million units over a period of 5 to 15 days. Thereafter 6 million units were given in 15 days. Fever therapy was administered in amounts equivalent to one-half the usually accepted course of therapy, e. g., five to

[1] From the Boston Psychopathic Hospital, Boston, Mass.

seven paroxysms of malaria, or 20 hours of artificial fever above 105° F. (rectal). One-fourth of the total group was given penicillin alone; the remainder was given penicillin combined with fever therapy. The clinical status of these cases is presented in table 2.

Table 2.—*Clinical status of 377 neurosyphilis patients treated with penicillin, with or without fever, and followed from 3 months to 5 years*

Diagnosis	Total patients	Clinical status		
		Improved	Unimproved	Unchanged
General paresis	272	194	78	0
Juvenile paresis	13	7	3	3
Tabes	35	28	4	3
Primary optic atrophy	18	7	7	4
Meningovascular neurosyphilis	21	17	2	2
Asymptomatic neurosyphilis	18	0	0	18
Total	377	253	94	30
		Percent 67	*Percent* 25	*Percent* 8

Criteria for Evaluation

In order to obviate some of the difficulties in clinical evaluation, we have elected to lay emphasis upon the capacity of the patient to be out of the hospital and to be employed. If a patient has shown no material change in his condition, but is well enough to be out of the hospital and is gainfully employed, he is placed in the improved group for statistical purposes. On the other hand, if a patient is living at home, yet has shown no improvement and is not gainfully employed, he is grouped as unimproved. A hospitalized patient is recorded in the unimproved group until he actually is in the community, even though his clinical condition may have shown improvement. Cases of asymptomatic neurosyphilis whose cerebrospinal fluid has become normal are recorded in the improved group, for they are all home and working and have remained clinically well.

Clinical Results

We are confining this report of the results of treatment to those patients followed 1 year or longer. Table 3 is a summary of the present clinical status of 320 cases of neurosyphilis of several clinical varieties followed from over 1 to 5 years in accordance

with clinical condition, at home, or in the hospital, and working or not working.

Two hundred twenty-nine (72 percent) of the cases improved, and 91 (28 percent) are unimproved.

Table 3.—*Over-all status of 320 neurosyphilis patients followed from 1 to 5 years*

Group	Status	Number
Improved	Improved; home; working	190
	Improved; home; not working	16
	Unimproved; home; working	9
	Asymptomatic; home; working	14
	Total	229
		Percent 72
Unimproved	Unimproved; home; not working	18
	Hospital cases	73
	Total	91
		Percent 28

Since the vast majority of the cases treated by us have been general paretics, the body of this paper will be concerned chiefly with this group. Two hundred thirty-three paretic patients have been followed for more than 1 year. The clinical syndromes of these, subdivided into four diagnostic categories, is presented in table 4. These data are of particular importance, for they indicate that psychiatric symptoms are of prognostic value. Patients with psychoses predominantly affective in type showed the best results. All such cases improved. Sixty-seven percent of the cases with psychosis of simple dementia are improved. Only 25 percent of the schizoid cases are improved. Patients were classified in the group "Minimal symptoms" if mental changes were insufficient to warrant legal commitment. This group of patients showed excellent results. Eighty-nine percent of them improved.

Table 4.—*Clinical status of 233 paretic patients followed over 1 year*

Types of psychosis	Total number	Improved group	
		Number	*Percent*
Manic-depressive [1]	22	22	100
Minimal symptoms	55	49	89
Simple dementia	110	74	67
Schizophrenic-like [1]	46	12	25

[1] Cases receiving antisyphilitic re-treatment and electric shock are included here.

Analysis of Therapeutic Failures

It is felt that a study of the cases which failed to improve would be useful in explaining some of the factors which contribute to the failure. The failure cases in our series are classified into two groups:

1. Patients who remain hospitalized after 1 year.
2. Patients who, although they are at home, are yet clinically unimproved and not working. These may be cases with residual dementia arrested.

Hospitalized Cases

The largest failure group is the one which is hospitalized. Seventy general paretic patients, followed for over 1 year, have been studied. Of this group 37 are of the simple demented type of psychosis, and 33 have a psychosis with schizophrenic features. The hospitalized demented group constitutes 33 percent of all (110) the demented cases which have been treated with penicillin and followed 1 year and more, in marked contrast to the hospitalized schizophrenic-like group which constitutes 71 percent of all (46) such cases treated.

The significant difference between both groups lies in the duration of symptomatology prior to penicillin treatment. Fair results (49 percent of the cases showed some improvement) were obtained in the demented group when treatment was given within 1 year from the onset of symptomatology, in contrast to the schizophrenic-like group, in which poor results (only 9 percent of the cases showed some improvement) were obtained regardless of the duration of symptomatology.

The cerebrospinal fluid changes of the hospitalized cases closely approximate the pattern of improvement generally reported by all investigators.

Unimproved, Home, Not-Working Group

The second group of clinical failures with penicillin treatment consists of 17 cases followed over 1 year and classified as clinically unimproved, at home, but not gainfully employed. A review of the diagnosis of each case as outlined in table 5 indicates that there is a severe physical handicap present in 15 of the 17 cases. The duration of the symptomatology prior to the Boston Psychopathic Hospital hospitalization in most of the cases was 2 years or over. Twelve of the cases received fever treatment in addition to penicillin. Apart from one juvenile paretic, most of the patients were in their fourth or early part of their fifth decade. The reasons for not working are enumerated for each patient, and, for the most part, they are due to residuals of severe organic pathology,

Table 5.—*Analysis of clinical data of 17 neurosyphilis patients who are clinically unimproved, at home, and not working and followed from 14 to 56 months*

Pt. No.	Diagnosis	Treatment	Reason for not working
1	Primary optic atrophy	Penicillin and malaria	Totally blind.
2	Primary optic atrophy	Penicillin and fever cabinet	Totally blind.
3	Tabes, optic atrophy	Penicillin and malaria	Totally blind, ataxia.
4	Tabes, optic atrophy	Penicillin and fever cabinet	Dizzy spells, partial blindness, neuritis.
5	Tabes, optic atrophy	Penicillin	Partially blind, leg pains.
6	Tabes	Penicillin	Ataxia.
7	Meningovascular	Penicillin	Aphasia, epilepsy.
8	Meningovascular (Erb's)	Penicillin and fever cabinet	Cannot walk, dizzy spells.
9	Juvenile paresis	Penicillin and malaria	Epilepsy, feeble-minded.
10	Paresis	Penicillin and malaria	Hemiplegia, aphasia.
11	Paresis	Penicillin and malaria	Cerebellar signs, spasticity, dementia.
12	Paresis	Penicillin and malaria	Severe deterioration, (benevolent family).
13	Taboparesis	Penicillin and malaria	Dementia.
14	Taboparesis	Penicillin	Severe dysarthria.
15	Taboparesis	Penicillin and malaria	Schizophrenie (benevolent family).
16	Taboparesis	Penicillin and malaria	Paranoid.
17	Taboparesis	Penicillin	Dysarthria, somatic complaints.

except in two cases of paranoid psychosis. The spinal fluid cell count was normal in all instances, and in only 3 patients was the protein abnormal; but, it was considerably improved over that present prior to therapy. It is quite apparent that no antisyphilitic treatment can be expected materially to improve these patients. They are failures to penicillin treatment not because of significant cerebrospinal fluid abnormalities, but because they have organic residuals of neurosyphilis.

Analysis of Cases Requiring Additional Therapies

A number of cases were treated a second or a third time with penicillin, and some were given fever treatment and electroshock therapy after inadequate response to penicillin. Since these cases constitute a group which for one reason or another were thought to need more treatment, they were at the time failures in therapy. The following is an analysis of these cases.

Re-Treatment Cases

A total of 79 patients who were re-treated with either penicillin and/or fever therapy have been followed for over 1 year. Fifteen patients (19 percent) have died, and 3 have been lost from follow-up. Forty-six (58 percent) were re-treated for clinical indica-

tions, 21 (26 percent) for persistence of cerebrospinal fluid abnormalities, and 14 (16 percent) for other reasons, that is, penicillin given in other hospitals or clinics without our knowledge of the indications and observations, and for medical and surgical conditions apart from syphilis. It is significant to note that over half of the cases were re-treated for clinical reasons and of this group 9 (16 percent) died. Paresis was considered a contributory cause in 4 of the deaths.

The status of the 55 cases who were re-treated either on a clinical basis or because of cerebrospinal fluid abnormalities were reviewed (table 6). Fifteen (75 percent) of the cases re-treated on the

Table 6.—*Clinical status of 55 penicillin re-treated cases followed over 1 year from initial penicillin treatment*

Present clinical status	Re-treated on CSF basis (20 cases)		Re-treated on clinical basis (35 cases)	
	Number	*Percent*	*Number*	*Percent*
Improved	15	75	17	49
Unimproved	5	25	18	51

basis of abnormalities or relapse in the cerebrospinal fluid are clinically improved after 1 year of follow-up. Seventeen (49 percent) of the cases re-treated on the basis of clinical considerations are improved after follow-up of a year or more. Analysis of the 18 cases who remain unimproved reveals that 15 are general paretics of the simple demented or schizophrenic-like types of psychosis. The spinal fluids of all cases followed the usually reported improvement patterns.

Cases Treated with Electroshock Therapy

Twenty-five paretic patients were treated with electroshock therapy in addition to penicillin and fever because of poor clinical response. In several instances it was indicated as a life-saving measure. Twenty of the group are living, and 5 are deceased (3 of medical causes and 2 suicides). The two suicidal cases were depressed patients who were inadequately treated with electroshock therapy and discharged from the hospital upon the insistence of relatives. Of the 20 living cases (table 7), 12 were characterized by predominantly affective syndromes. All improved with electroshock therapy and were discharged to their homes. The remaining 8 cases showed predominantly schizophrenic symptomatology. These remain unimproved and are hospitalized. The cerebrospinal fluid of all cases improved satisfactorily. These results suggest that:

Table 7.—*Results of electro-shock therapy on 20 living penicillin-treated paretic patients*

Clinical status	Psychosis with symptomatology predominantly			
	Affective type (12 cases)		Schizophrenic type (8 cases)	
	Number	*Percent*	*Number*	*Percent*
Improved and home	12	100	0	
Unimproved and hospitalized	0		8	100

(*a*) In the paretic patients showing an affective syndrome, electroshock therapy tends to relieve symptoms quickly.

(*b*) In the paretic patients showing a schizophrenic syndrome, electroshock therapy is of little benefit.

A study of the prepsychotic personality traits of the patients is in progress and indicates that there is a difference between the prepsychotic personality in cases of general paresis with a schizophrenic-like syndrome and those with a manic-depressive syndrome. This suggests that the symptomatology has its roots in the personality of the patient and the prognosis relates in part at least to his early personality structure.

Summary and Conclusions

1. Four hundred forty-six patients with neurosyphilis have been treated with penicillin from February 1, 1944, to March 1, 1949. Three-fourths of the patients had general paresis.

2. Penicillin was given in 3- or 6-million unit dosages over intervals of 5 to 16 days. The majority of the patients were also given fever, either malaria or fever cabinet, in approximately one-half the usually accepted course.

3. Seventy-two percent of the neurosyphilis patients followed from 1 year to 5 years were at home and at full working capacity.

4. Fifty-two (12 percent) patients died, but in only 16 can death be attributed to the syphilitic process. The adjusted mortality rate is 4 percent. Seventeen patients (4 percent) have been lost to clinical follow-up.

5. Analysis of the present clinical status of 233 paretic patients followed over 1 year indicates that the type of psychosis present prior to treatment is of value prognostically. Psychoses of the affective type have an excellent prognosis—all cases improved—although a few cases required electric shock therapy in addition to the penicillin. The demented group offers a fair prognosis—67 percent of the cases improved. The schizophrenic-like group offers the poorest prognosis—only 25 percent are improved.

6. Analysis of the clinical failures to penicillin therapy reveals that the failure of the cases to improve is ascribable to either or both of (1) the type of psychosis present prior to treatment, and (2) residuals of severe organic pathology.

7. Of the 35 cases re-treated for clinical considerations, 49 percent are improved after 1 year of follow-up. Of the 20 cases re-treated on the basis of persistence of cerebrospinal fluid abnormalities or relapse, 75 percent are improved. All but a few of the unimproved group are general paretics of the simple demented and schizophrenic-like types. The spinal fluid of all groups followed the usually reported improvement patterns.

8. Of the 20 living cases who were given electric shock therapy in addition to penicillin and malaria, all of the affective group are improved and at home, in marked contrast to all of the schizophrenic-like group who are unimproved and are hospitalized. These results are consistent with those usually found in the affective and schizophrenic psychoses without general paresis.

9. The results as a whole suggest that the treatment used, namely penicillin alone, penicillin with fever and also repeated courses of both, brought an arrest of the pathological process to all cases. The lack of associated clinical improvement in some of these cases is due to (1) neurological residuals of the disease, and (2) the type of psychosis present at time of treatment.

Acknowledgment

The authors wish to express appreciation to Lida R. Carmen, psychiatric social worker, and to Dr. Nicholas Fiumara, Division of Venereal Diseases, Massachusetts Department of Public Health, for their cooperation in maintaining the high rate of follow-up of patients.

Neurosyphilis III. Evaluation After Three Years of Treatment with Penicillin Alone and with a Combination of Penicillin and Malaria[1]

A. C. Curtis, W. T. Kruse, and D. H. Norton

Our third report is based on a study of 602 patients with various types of neurosyphilis who have been treated at the University Hospital with penicillin and penicillin plus malaria since 1944. It has been possible to follow 380 (63 percent) of these patients from 1 to more than 3 years after a single course of treatment.

No follow-up was obtained in 222 (37 percent) cases. Of this number 21 patients died (5 probably due to syphilis), 22 were re-treated elsewhere (often without adequate reason), 22 refused to return, and 157 either were followed for less than 9 months or the whereabouts of the patient was not known. The percentages of patients followed 1, 2, and 3 or more years was almost identical: 118 (31 percent) were followed for 1 year, 123 (32 percent) were followed 2 years, and 139 (37 percent) were followed for 3 or more years subsequent to treatment. Thirty-nine (10 percent) were observed for more than 3 years.

The number of patients who received the two types of therapy was about equal: 186 (49 percent) patients had penicillin alone, and 194 (51 percent) received combined therapy. Table 1 summarizes the numbers of patients in each of four diagnostic categories: asymptomatic neurosyphilis, meningovascular, tabes

Table 1.—*Types of neurosyphilitic involvement in 380 patients treated with penicillin and penicillin plus malaria*

Type of neurosyphilis	Followed 1 year			Followed 2 years			Followed 3 years or more		
	Number of cases	Treatment		Number of cases	Treatment		Number of cases	Treatment	
		Penicillin	Penicillin + malaria		Penicillin	Penicillin + malaria		Penicillin	Penicillin + malaria
Asymptomatic	10	4	6	23	15	8	15	12	3
Meningovascular	10	8	2	17	9	8	15	11	4
Tabes dorsalis	40	22	18	27	16	11	41	27	14
Paresis + taboparesis	58	15	43	56	26	30	68	21	47
Totals	118	49	69	123	66	57	139	71	68

[1] From the Department of Dermatology and Syphilology, Medical School, University of Michigan.

Presented at the Venereal Disease Symposium held in Washington, D.C., on April 7 and 8, 1949 under the auspices of the Syphilis Study Section of the National Institutes of Health.

This paper represents work done under a contract between the Committee on Medical Research, of the Office of Scientific Research and Development, and the University of Michigan; and later supported by a grant-in-aid from the Research Grants Office, National Institutes of Health, United States Public Health Service. Part of the expense for this study was defrayed by the Babcock Urological Research Fund.

dorsalis, and paresis plus taboparesis. One hundred eighty-two (47 percent) patients were classified as having paresis or taboparesis, and thus comprised about one-half of the entire group.

Method of Treatment

Treatment consisted of a total dosage of 4,000,000 units of aqueous penicillin given in doses of 40,000 units every 3 hours intramuscularly for 100 injections. When fever was given concurrently with penicillin, therapeutic tertian malaria was induced and the patient received 50 or more hours of fever above 103.5° F. rectally. As a rule, the penicillin injections were started after the patient had his first malarial chill.

Results

Because of the difficulty and inaccuracy of appraising clinical improvement or relapse in relationship to treatment, clinical evaluation was relegated to second place and the emphasis was placed on the objective spinal fluid findings. This is in accord with present day consensus, including that stated by Dattner (*1*).

Table 2 shows the posttreatment clinical and spinal fluid evaluation for the entire group of 380 patients followed from 1 to more than 3 years. In 1947 a report was made of 118 patients in this series who had been observed for 1 year following treatment. In this early preliminary report of 1 year's observation of a group of patients with central nervous system syphilis, a clinical superiority of 23 percent and a laboratory superiority of 19 percent was apparent when the combined method rather than the penicillin treatment alone was utilized (*2*).

One year later (*3*) an analysis of 223 patients was reported.

Table 2.—*Posttreatment evaluation of 380 patients followed 1 to 3 or more years*

Appraisal	Treatment	Improved		Unchanged		Worse		Total
		Number	Percent	Number	Percent	Number	Percent	
Clinical [1]	Penicillin	73	47	71	46	11	7	155
	Penicillin + malaria	75	42	90	51	12	7	177
Spinal fluid [2]	Penicillin	156	87	24	13	0	0	180
	Penicillin + malaria	175	91	18	9	0	0	193

[1] 48 patients with asymptomatic involvement were omitted.
[2] Patients with initial negative spinal fluids were omitted.

These patients were followed for 1 year and included those with initial negative spinal fluids. When the number of patients with initial negative spinal fluids was omitted there was a clinical superiority of 10 percent in the penicillin-alone group and only 2 percent superiority in spinal fluid improvement in the combined-therapy group. There was a 6-percent superiority in spinal fluid improvement for the combined therapy group of 104 patients followed for 2 years.

In the present analysis (table 2) derived from a study of 380 patients, there was a clinical superiority of 5 percent in favor of the penicillin-alone group and a 4-percent superiority in spinal fluid improvement in favor of the combined therapy group. These differences in groups of this size probably have no significance.

Table 3 illustrates the results of the clinical and spinal fluid evaluation of 139 patients in the present analysis who were followed for three or more years posttreatment. Here there was a 4-percent superiority in clinical evaluation for the penicillin-alone group and a 9-percent superiority in spinal fluid improvement for the combined-therapy group. Thus at the end of 3 years of observation, statistically, there was no important difference in the clinical and spinal fluid results obtained by the two types of therapy.

Table 3.—*Results of treatment of 139 patients with all types of C.N.S. involvement followed for 3 years or more*

Appraisal	Treatment	Improved		Unchanged		Worse		Total
		Number	Percent	Number	Percent	Number	Percent	
Clinical (excluding asymptomatic)	Penicillin	25	42	30	51	4	7	59
	Penicillin + malaria	24	38	38	57	3	5	65
Spinal fluid	Penicillin	54	76	17	24	0	0	71
	Penicillin + malaria	58	85	10	15	0	0	68

The response of the cell count, total protein, colloidal gold curve,[2] and quantitative Kahn serologic tests with the two different types of therapy is shown in figures 1, 2, 3, and 4. To make the average figures for the various spinal fluid tests statistically sounder, the curves (figs. 1, 2, 3, and 4) were derived from the spinal fluid findings in all 380 patients. It should be noted that the figures during the early posttreatment months carried more weight than those during the latter posttreatment months, when relatively

[2] Average of a total of all the figures of the colloidal gold test.

fewer patients contributed to the averages. Undoubtedly, this accounted for the occasional irregularities in an otherwise smooth curve at 36 and 48 months.

In general, the patients who showed greater deterioration clinically received combined therapy. This accounted for the slightly higher initial spinal fluid abnormalities, in most instances, among the penicillin-plus-malaria group. However, the curves (figs. 1, 2, 3, and 4) show that the two types of therapy produce approximately the same amount of depression of the spinal fluid abnormality regardless of the height of the initial abnormality. In addition, with longer posttreatment observation, the two curves tended to approximate each other.

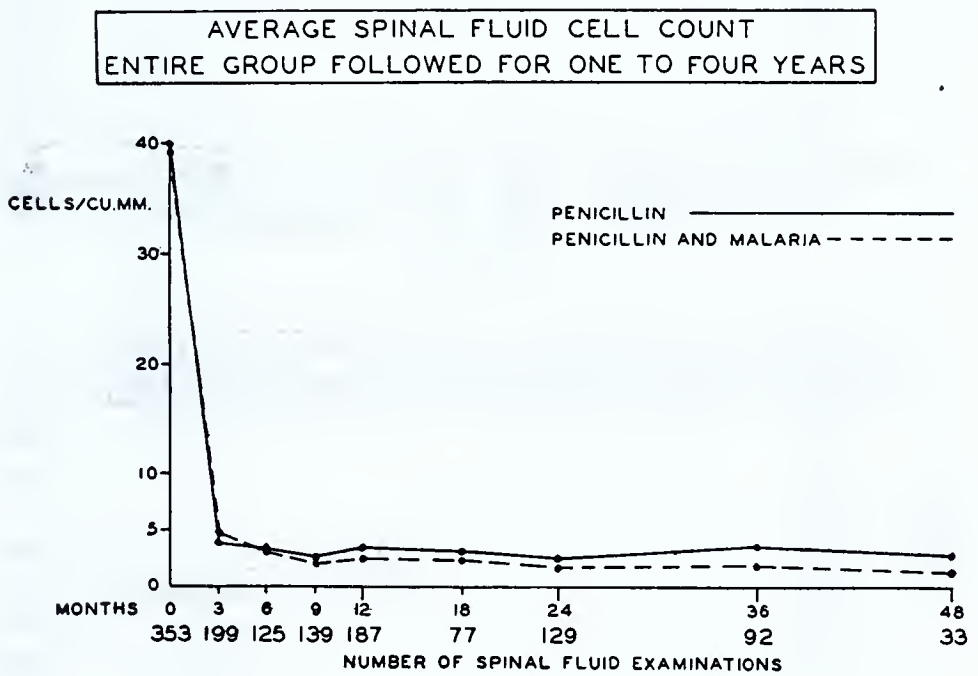


FIGURE 1.

There seems to be no definite opinion as to what comprises a normal spinal fluid. No doubt this diversity of opinion is due to the many variations in technic used in different laboratories. Stokes (*4*), in considering the spinal fluid quantitative protein, states that "the normal reading according to various authors ranges (Hinrichsen, 1941) from 25 to 75 mg. percent." Madonick (*5*) says, "we consider values below 50 mg. per 100 cc. as still being within normal limits." In our laboratories, using sulfosalicylic acid, we are of the opinion that readings between 40 and 50 mg. per 100 cc. are not abnormal. This impression is based

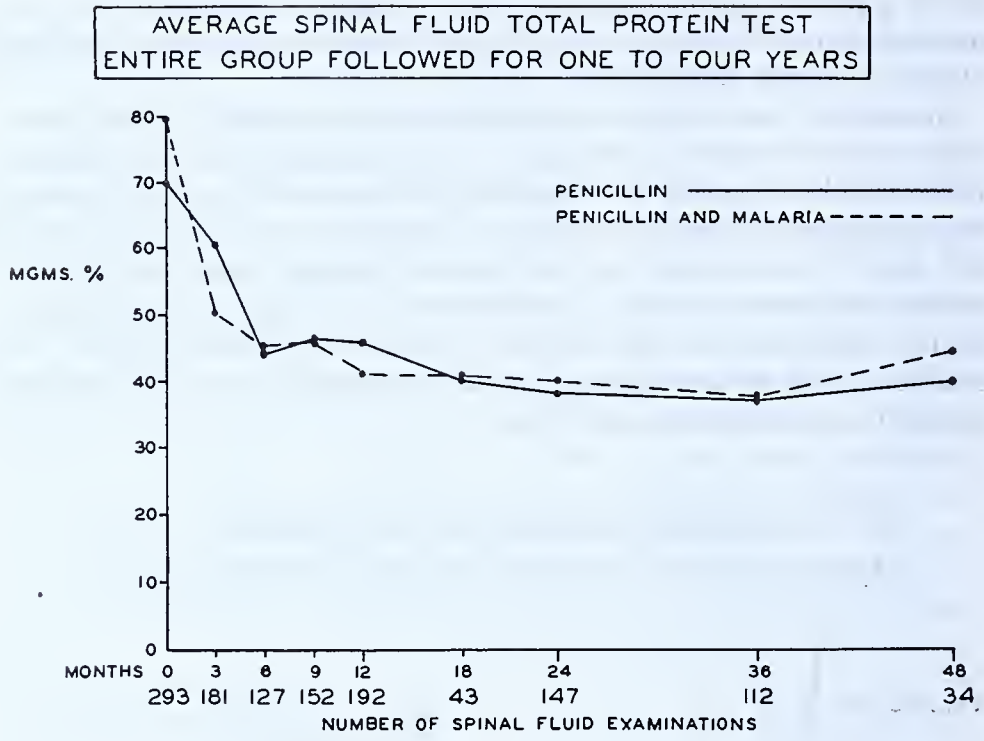


FIGURE 2.

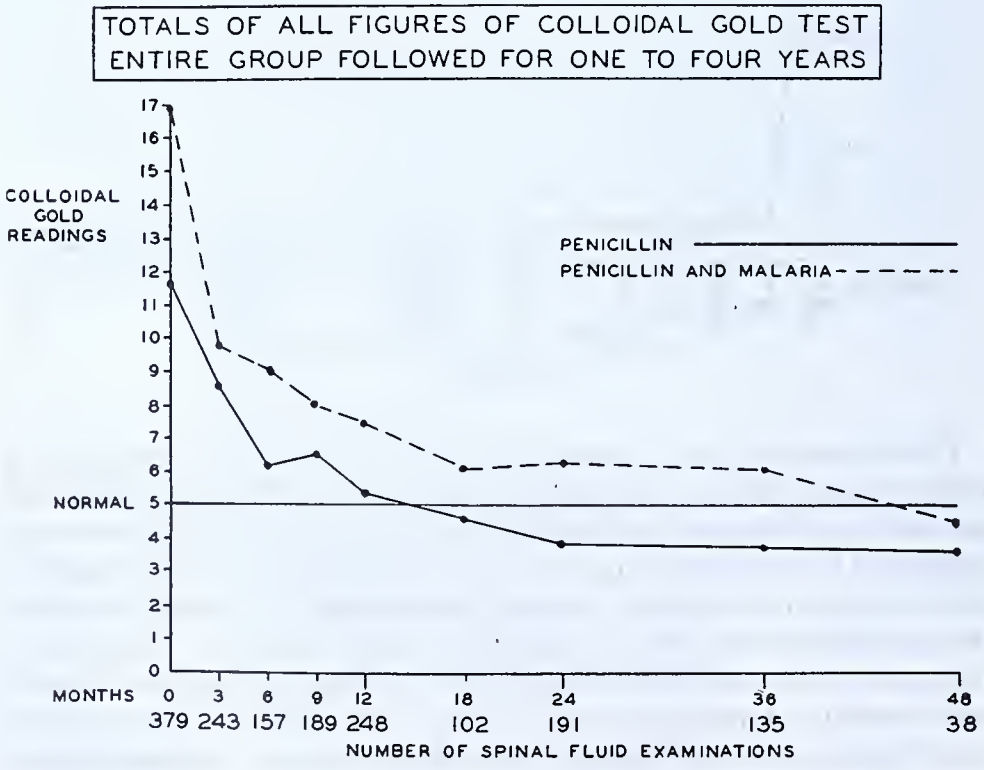


FIGURE 3.

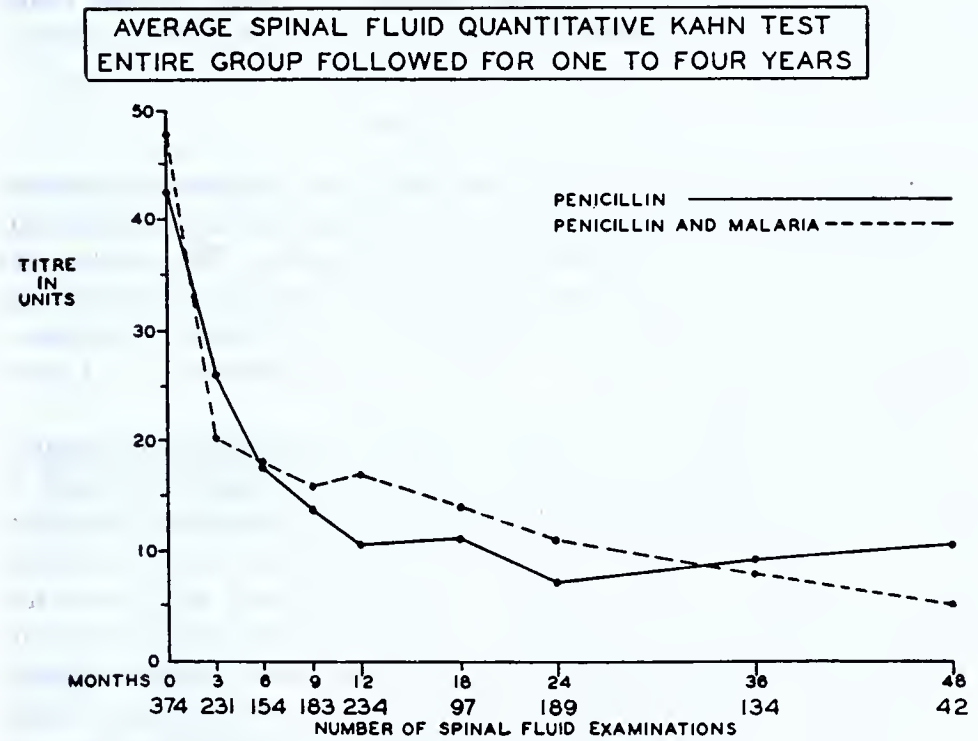


FIGURE 4.

on a short study of 100 "normal" spinal fluids from patients not infected with syphilis or any other specific central nervous system disease. The result showed a range between 15 and 60 mg. percent.

Stokes (4) has given 0112100000 (total of 5) as indeterminate for the colloidal gold reading and we have used this figure as the upper limit of normal. A cell count of 5 usually was considered the upper limit of normal. Using this criterion, the cell count became normal within 6 months, the total protein within 9 months, and the colloidal gold curve within 24 to 48 months. This occurred with both types of therapy.

Among 380 patients, there were 7 with initially negative spinal fluids. All of these patients had tabes dorsalis and treatment was instituted because of severe symptoms. There was improvement in 5 who had received penicillin alone, and in 1 who had received combined therapy.

In this group of 373 patients with initially abnormal spinal fluids, 78 (21 percent) became normal in all the spinal fluid components. Eight and five-tenths percent were normal at the end of 6 months, 5.8 percent became normal at the end of 12 months, 4.2 percent at 24 months, and 2.4 percent at 36 months. Generally,

those patients who had the least amount of initial spinal fluid abnormality became normal sooner than those with grossly abnormal spinal fluids.

Results—Paresis

In the 1948 reports (*3*) there seemed to be no great difference in the response of patients in the several diagnostic categories to penicillin alone or to penicillin plus malaria. The group of patients with paresis was the exception. Fifty-six patients who had either paresis or taboparesis and had been followed for 2 years showed 16-percent superiority in spinal fluid improvement in favor of combined therapy.

At the present time, 68 patients with paresis and taboparesis, followed for a minimum of 3 years, had a superiority of only 3 percent in spinal fluid improvement in favor of combined therapy (table 4). With a longer period of posttreatment observation it would appear that even in paresis, penicillin alone will prove as effective as penicillin plus malaria. These results would seem to substantiate an opinion which was expressed in our report of one year ago (*3*): "There may possibly remain some evidence that fever therapy plus penicillin is superior to penicillin alone in dementia paralytica. We have the impression that a longer period of observation after treatment, will show improvement from penicillin alone equal to that from combined therapy." Wong and Packer (*6*) have also concurred in this opinion, for they made an analysis of the reversals in the complement-fixation test in spinal fluid and blood following penicillin and penicillin plus malaria in 120 patients with neurosyphilis.

The converse, however, is expressed by Kopp, Rose, and Solomon (*7*), who conducted a study of 394 (77 percent paretic) patients with neurosyphilis, treated with penicillin alone or with penicillin plus one-half of the usually accepted course of fever (malaria). They concluded that penicillin, given over a 15-day period plus a

Table 4.—***Results of treatment of 68 patients with paresis and taboparesis followed for 3 or more years***

Appraisal	Treatment	Improved		Unchanged		Worse		Total
		Number	Percent	Number	Percent	Number	Percent	
Clinical	Penicillin	12	57	9	43	0	0	21
	Penicillin + malaria	19	41	25	53	3	6	47
Spinal fluid	Penicillin	18	86	3	14	0	0	21
	Penicillin + malaria	42	89	5	11	0	0	47

short course of malaria was "equal to or superior to any treatment thus far known in late symptomatic neurosyphilis."

Figures 5, 6, 7, and 8 show the response of several components of the spinal fluid in 182 patients with paresis or taboparesis who were followed for three or more years. The general trend was the same as in the analysis of the entire group, showing little or no difference between the two types of therapy. There was some irregularity in the curves but here the figures were not as statistically sound because of the smaller number of spinal fluid examinations.

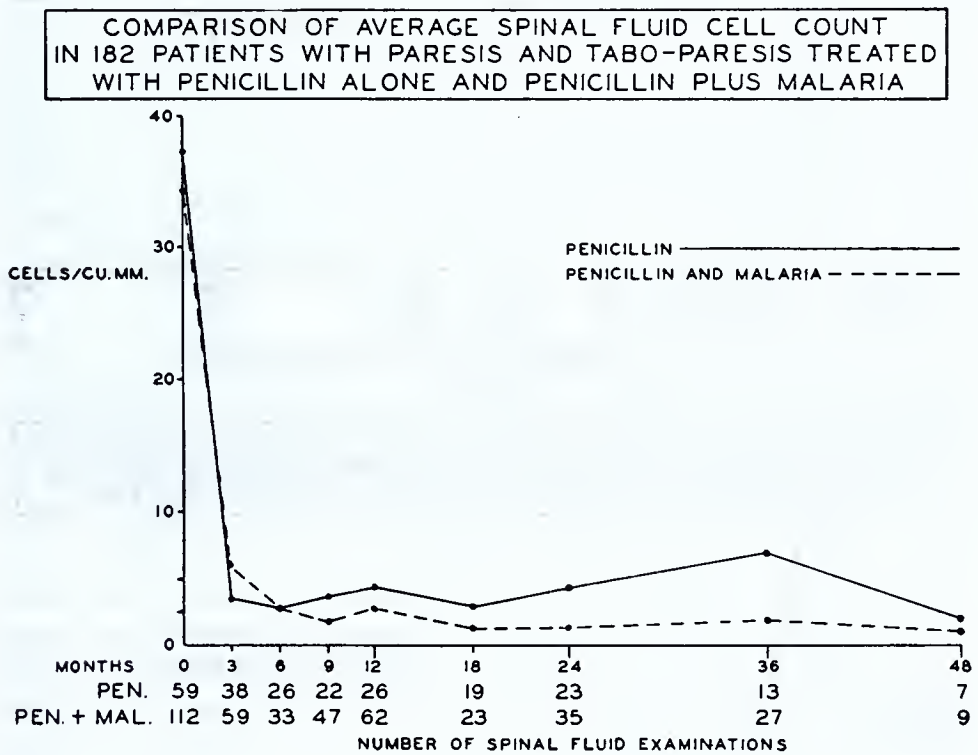

COMPARISON OF AVERAGE SPINAL FLUID CELL COUNT
IN 182 PATIENTS WITH PARESIS AND TABO-PARESIS TREATED
WITH PENICILLIN ALONE AND PENICILLIN PLUS MALARIA
CELLS/CU.MM.
40
30
20
10
0
PENICILLIN
PENICILLIN AND MALARIA
MONTHS 0 3 6 9 12 18 24 36 48
PEN. 59 38 26 22 26 19 23 13 7
PEN. + MAL. 112 59 33 47 62 23 35 27 9
NUMBER OF SPINAL FLUID EXAMINATIONS

FIGURE 5.

Comment

There have been five patients followed by us, whose spinal fluid formulae became worse after treatment. Of these, three were treated with penicillin alone and two with combined therapy. These relapses occurred during the first posttreatment year. There have been no patients who showed a progression in the spinal fluid abnormalities during the second and third posttreatment years. The five patients with spinal fluid relapses were re-treated and have since shown improvement in the spinal fluid.

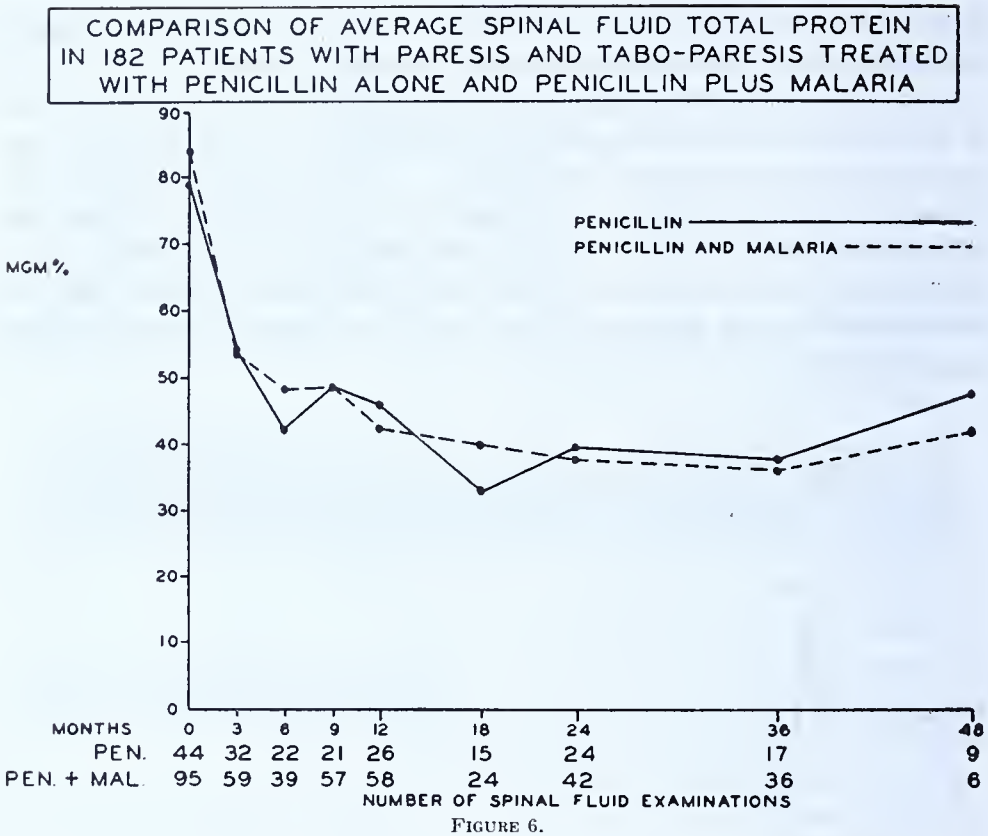

COMPARISON OF AVERAGE SPINAL FLUID TOTAL PROTEIN IN 182 PATIENTS WITH PARESIS AND TABO-PARESIS TREATED WITH PENICILLIN ALONE AND PENICILLIN PLUS MALARIA
MGM %
PENICILLIN
PENICILLIN AND MALARIA
90
80
70
60
50
40
30
20
10
0
MONTHS 0 3 6 9 12 18 24 36 48
PEN. 44 32 22 21 26 15 24 17 9
PEN. + MAL. 95 59 39 57 58 24 42 36 6
NUMBER OF SPINAL FLUID EXAMINATIONS

FIGURE 6.

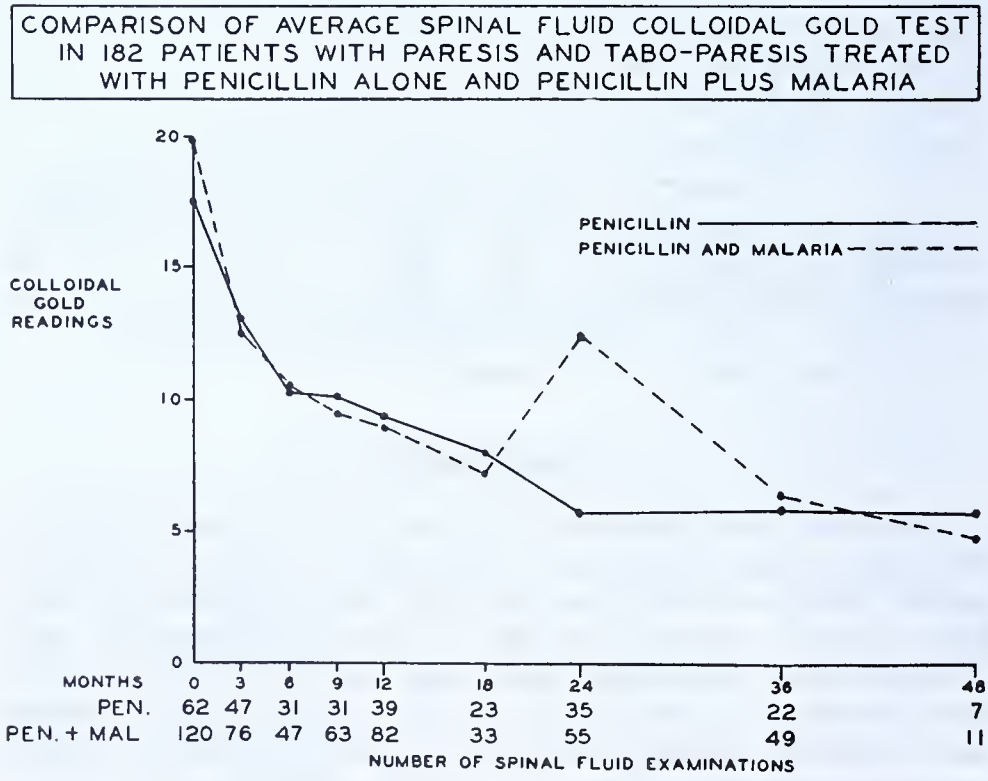

COMPARISON OF AVERAGE SPINAL FLUID COLLOIDAL GOLD TEST IN 182 PATIENTS WITH PARESIS AND TABO-PARESIS TREATED WITH PENICILLIN ALONE AND PENICILLIN PLUS MALARIA
COLLOIDAL GOLD READINGS
PENICILLIN
PENICILLIN AND MALARIA
20
15
10
5
0
MONTHS 0 3 6 9 12 18 24 36 48
PEN. 62 47 31 31 39 23 35 22 7
PEN. + MAL 120 76 47 63 82 33 55 49 11
NUMBER OF SPINAL FLUID EXAMINATIONS

FIGURE 7.

COMPARISON OF AVERAGE SPINAL FLUID QUANTITATIVE KAHN TEST IN 182 PATIENTS WITH PARESIS AND TABO-PARESIS TREATED WITH PENICILLIN ALONE AND PENICILLIN PLUS MALARIA

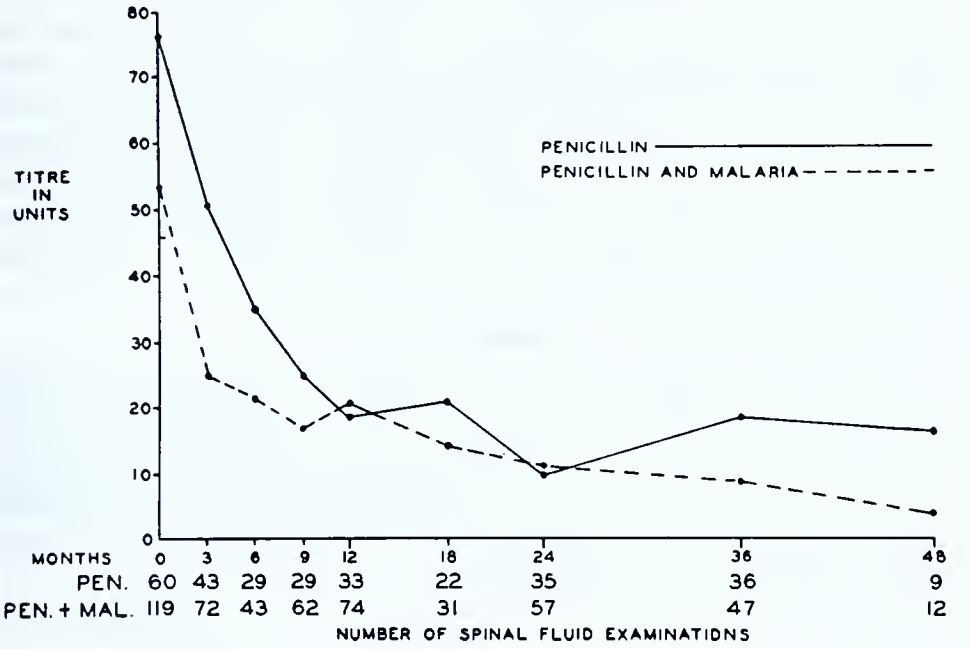


FIGURE 8.

From a total of 602 patients, 62 (10 percent) have been re-treated for one or another reason but not necessarily because of progression of the syphilitic disease. Forty-one (66 percent) were re-treated within 1 year, 15 (24 percent) were re-treated within 2 years, and 6 (10 percent) were re-treated within 2 to 4 years. Thirty-four (55 percent) of the 62 patients in this group manifested progressive symptoms, 6 (10 percent) received post-operative penicillin, and 22 (35 percent) were given further therapy by physicians not cognizant of the value of penicillin in the treatment of central nervous system syphilis. If the 34 patients with progressive symptoms were considered as failures, and probably all were not, then the failure rate of 602 patients was 5.6 percent.

In the group of 380 patients with adequate follow-up there were 22 (6 percent) patients who were clinically worse following therapy. Eleven of the 22 became worse within the first post-treatment year, 7 within 2 years, and 4 within 4 years. Ten of these twenty-two patients received penicillin alone and 12 received combined therapy. The failure rate for this group of 380 patients was 6 percent. Kierland, O'Leary, and Underwood (*8*) also reported a 6-percent failure in clinical response for a series of 63 patients with symptomatic neurosyphilis receiving penicillin plus malaria.

There seemed to be no correlation between the development of spinal fluid serologic negativity and blood serologic negativity. In this series of 380 patients, 21 percent developed negative spinal fluid tests and 17 percent developed negative blood tests when the initial examinations had been positive. The spinal fluid and blood serologic tests reverted to negative in only 23 (6 percent) patients after both tests had been initially positive. Spinal fluid negativity preceded blood negativity in 9 cases. It occurred at the same time as the blood in 9 cases and followed blood negativity in 4 cases. This lack of correlation has been observed by many on previous occasions.

Summary

1. This is a report on the posttreatment observation of 380 patients with various types of neurosyphilis who have received either penicillin alone or a combination of penicillin plus malaria.

2. Approximately one-third of these patients have been followed for 1 year, one-third for 2 years, and one-third for 3 or more years after a single course of treatment.

3. The clinical failure rate is 6 percent with either type of therapy.

4. Patients with various types of central nervous system syphilis, including paresis, respond equally well to penicillin alone and to penicillin plus malaria. This response is shown in both clinical and spinal fluid improvement.

References

1. Dattner, B.: Treatment of neurosyphilis with penicillin alone. Am. J Syph., Gonor. & Ven. Dis., 32: 399, 1948.
2. Curtis, A. C.; Burns, R. E.; Norton, D. H.: Neurosyphilis: Treatment with penicillin alone and with a combination of penicillin and malaria. Am. J. Syph., Gonor. & Ven. Dis., 31: 618, 1947.
3. Curtis, A. C.; Horne, S. F.; Norton, D. H.: Neurosyphilis: Evaluation after two years of treatment with penicillin alone and with a combination of penicillin and malaria. Am. J. Syph., Gonor. & Ven. Dis., 32: 546, 1948.
4. Stokes, J. H.; Beerman, H.; Ingraham, N. R., Jr.: Modern Clinical Syphilology. Ed. 3, 1946. W. B. Saunders Co., Philadelphia and London. P. 114.
5. Madonick, M. J.; Savitsky, U.: The relation between the Pandy test and total protein content of spinal fluid. J. Lab. & Clin. Med., 29: 542, 1944.
6. Wong, Y. T.; Packer, H.: Spinal fluid and blood complement fixation reversal in neurosyphilis. Am. J. Syph., Gonor. & Ven. Dis., 32: 565, 1948.
7. Kopp, I.; Rose, A. S.; Solomon, H. C.: The treatment of late symptomatic neurosyphilis at the Boston Psychopathic Hospital: A study of the results of penicillin therapy in 394 patients treated between February, 1944 and March, 1948. Am. J. Syph., Gonor. & Ven. Dis., 32: 509, 1948.
8. Kierland, R. R.; O'Leary, P. S.; Underwood, L. J.: The treatment of neurosyphilis with a combination of malaria and penicillin. Am. J. Syph., Gonor. & Ven. Dis., 32: 470, 1948.

Penicillin Failures in Neurosyphilis[1]

Bernhard Dattner

Treatment of an infectious process must be considered as effective if the invading micro-organisms have been destroyed, without harm to the patient. This does not mean, however, that pathologically and clinically the premorbid status has been secured. A complete restoration of function will be obtained in those patients only in whom no irreversible damage of the afflicted tissues had taken place. This is a universally accepted fact. But when it comes to the discussion of therapeutic effects in neurosyphilis there are many who expect the same degree of clinical recovery in such divergent pathologic syndromes as, e.g., early meningovascular syphilis and tabes. This is, however, not the only objection against the evaluation of any therapy of neurosyphilis from a clinical point of view. Such an approach involves consideration of fluctuating and flexible factors such as lightning pains, impotence, epileptic seizures, mood disorders, working capacity, etc., the appraisal of which must remain highly subjective and, therefore, liable to bias. For these reasons there is still much controversy with regard to the *clinical* results of penicillin therapy in neurosyphilis.

Anticipating these difficulties long known to us from previous experience, we at Bellevue Hospital relied exclusively on the results of the spinal fluid tests in the follow-up of our patients, because we consider them, as is well known, an *objective* index of therapeutic response or failure.

It is very much in favor of our concept that there is almost unanimous agreement on the profound effect of penicillin on the so-called spinal fluid formula. All authors confirm our impressions, gained more than 20 years ago in the observation of malaria-treated patients, that following successful treatment there is a rapid decrease of lymphocytosis and a gradual decline in the values of all the tests commonly performed on the spinal fluids of syphilitics. As mentioned especially by Stokes and his co-workers there is practically no difference between the response of patients with asymptomatic and those with parenchymatous neurosyphilis. If the spinal fluid findings reflect pathologic changes initiated by the infectious agent—and there is no doubt in our minds that they do so—then there must be an identical response to effective ther-

[1] From the Departments of Neurology, and Dermatology and Syphilology, New York University College of Medicine; and the Departments of Neurology, and Dermatology and Syphilology, Third Medical Division (New York University), Bellevue Hospital and The Rapid Treatment Center, Bellevue Hospital, New York, N. Y. Aided by grants from the U. S. Public Health Service.

apy in all forms of neurosyphilis since they are all caused by the same spirochetes.

For the reasons given it is not the purpose of this paper to report the results of penicillin therapy on the clinical manifestations of our patients with the various forms of neurosyphilis. We have treated more than 500 patients in the last 5 years. Only 388 form the basis for our discussion of failures of penicillin therapy. Failure of therapy was assumed in the presence of spinal fluid findings indicating persisting activity of the syphilitic process, that is, pleocytosis and abnormal protein values. A few cases were re-treated solely because of a high cell count although all the other tests indicated an abating process.

The figures given for the patients observed from 6 to 56 months do not include the 117 patients who were lost or died, among whom there must have been more failures. We believe, however, that the number of patients followed up for more than 12 months is large enough to draw some valid conclusions, since there are only rare exceptions where an "inactive" spinal fluid reverts to an active one 12 months after termination of treatment.

From table 1 it may be seen that of the 388 patients with active spinal fluid findings only 43 failed to respond to the first course of intramuscular penicillin injections, varying in amounts from 2 to 9 million units. Of these 43, however, 24 responded favorably to a second course of penicillin, usually given in higher amounts than the first one. No detailed analysis of the remaining 19 failures can be given because of lack of time. We single out for demonstration 3 patients (tables 2, 3, 4), the only ones who exhibit an active spinal fluid syndrome in spite of repeated courses of penicillin.

A closer scrutiny of these tables will reveal, first, that they concern patients with asymptomatic neurosyphilis, one of them in the

Table 1.—*Failure rate of patients with spinal fluid findings indicating activity following first course of treatment observed over a period of from 6 to 56 months*

Diagnosis	Number of patients	Failures	Successfully re-treated
Asymptomatic	89	12	7
Meningovascular	82	13	7
Tabes dorsalis	79	7	5
Dementia paralytica	61	6	3
Taboparesis	27	0	0
Optic atrophy	37	3	1
Erb	13	2	1
Total	[1]388	43	24

[1] Of the 388 patients, 331 have been followed from 12 to 56 months.

earliest stage, who proved resistant even to high amounts of penicillin, and secondly, that the spinal fluid findings of each of the patients showed some impact of the treatment on the cell count and/or the other parts of the spinal fluid syndrome. This was, however, temporary only and suggests that more intensive treatment might have produced a complete and permanent arrest of the process.

Table 2.—*E.B., age 20, Negro male, asymptomatic neurosyphilis, 1943 positive STS—hip and arm injections for 9 months*

Test No.	Date	Blood Wassermann	Spinal fluid Wassermann	Cells	Total protein	Colloidal Gold
	1946					
1	May 22	[1] 210	[1] 69	364/3	50	[2] 148
	May 20 to June 8	6 million units aqueous penicillin (13 days)				
	1947					
2	March 29	94	36	2,880/3	68	120
	March 29 to April 23	8 million units aqueous penicillin (25 days)				
	1948					
3	February 11	85	61	1,000/3	55	114
	February 11 to March 6	15 million units P.O.B. penicillin (25 days)				
4	May 6	55	17	33/3	45	51
5	October 8	67	33	120/3	53	100
	1949					
6	February 14	67	47	1,194/3	68	98
	March 1 to March 30	30 million units procaine penicillin (30 days)				
7	March 21	60	19	242/3	43	72
8	March 29	59	19	87/3	38	64

[1] Titered in units.

[2] The figure given represents the sum of readings in all 10 tubes by the new Lange method.

Table 3.—*F.O., age 28, Negro male, treated for primary and secondary syphilis with asymptomatic neurosyphilis from February 26, 1946 to March 6, 1946 with P.O.B. 4.8 million units*

Test No.	Date	Blood Wassermann	Spinal fluid Wassermann	Cells	Total protein	Colloidal Gold
	1947					
1	August 27	[1] 19	Negative	104/3	22	[2] 130
	August 26 to September 12	6 million units aqueous penicillin (17 days)				
	1948					
2	January 5	12	Negative	56/3	24	109
3	January 30	9	Negative	83/3	21	112
	January 30 to February 13	9 million units P.O.B. penicillin (15 days)				
4	May 20	8	Negative	135/3	46	141
	June 23 to July 12	30 million units aqueous penicillin (19 days)				
	1949					
5	March 22	5	Negative	26/3	19	100

[1] Titered in units.

[2] The figure given represents the sum of readings in all 10 tubes by the new Lange method.

Table 4.—*E.J., age 34, Negro male, asymptomatic neurosyphilis, 1944, positive STS from March 1944 to March 1947, received weekly arm and hip injections*

Test No.	Date	Blood Wassermann	Spinal fluid Wassermann	Cells	Total protein	Colloidal Gold
	1947					
1	November 22	[1] 7	[1] 7	137/3	38	[2] 128
	November 22 to December 6	9 million units P.O.B. penicillin (15 days)				
	1948					
2	March 10	5	7	11/3	44	114
3	April 15	6	8	428/3	42	127
	April 15 to April 29	9 million units P.O.B. penicillin (15 days)				
4	July 8	4	3	14/3	38	90
5	October 7	3	5	244/3	48	120
6	November 4	4	5	400/3	42	113
	November 6 to December 14	12 million units procaine penicillin (39 days)				
	1949					
7	February 24	2	4	143/3	38	118

[1] Titered in units.

[2] The figure given represents the sum of readings in all 10 tubes by the new Lange method.

From our studies we can draw the following conclusions:

1. Penicillin therapy of all types of neurosyphilis, if evaluated from the laboratory point of view, proved at least equally as effective as all previously used forms of treatment. It may be said in parenthesis that in our experience the same holds true for the clinical aspect.

2. More than half of the 43 patients who failed with one course responded favorably to a second course of penicillin given in higher amounts.

3. So far, our files contain only three patients who failed even with repeated courses of penicillin. This is most probably due to underdosage of penicillin.

4. Until there is some way of assaying the sensitiveness of spirochetes to penicillin, we may expect some therapeutic failures.

Pathological Observations in Penicillin-Treated Neurosyphilis [1]

George D. Gammon, F. H. Lewey, H. Dillon, G. Schwarz, and John H. Stokes

The impressive body of evidence, both serologic and clinical, of the effectiveness of penicillin therapy in neurosyphilis has not yet received anatomic verification. This report of the autopsy material from nine cases provides the beginning of such a study. Although small and containing few cases which may be considered crucial, the material indicates certain conclusions which may have been anticipated from clinical results.

A second part of the material consists of a case in which, despite positive Kolmer and colloidal mastic tests, the diagnosis of syphilis was doubted on the basis of a clinical picture of acute multiple sclerosis rather than neurosyphilis. Autopsy on this case, here reported, has confirmed the absence of lesions which would be attributed to lues.

Material

Of about 518 cases of neurosyphilis treated since November 1943, 32 have died of the causes indicated (table 1). Sixteen of them came to autopsy. In eight this was complete, but eight examined elsewhere did not include the nervous system. The material has not yet been studied for spirochetes.

Table 1.—*Cause and place of death and number of autopsies performed in 32 cases of neurosyphilis treated since November 1943*

Cause of death	Number	Place of death		Number of autopsies
		Hospital	Home	
Total	32	20	12	16
Cardiovascular disease:	13			
Cerebral accident	4			
Cardiac and hypertension	7			
Pulmonary	2			
Paresis	3			
Accidents	3			
Associated disease	9			
Unknown	4			

[1] From the Hospital of the University of Pennsylvania. Supported in part by Kirby-McCarthy Fund.

Paresis

Case 1 (No. 262).—A 52-year-old female with taboparesis of the agitated-depression type was treated 1 month after onset of mental symptoms with 2.4 million units of penicillin. The psychosis flared up and she died within 3 weeks. Autopsy revealed the typical changes of active paresis.

Case 2 (No. 84).—A male, 58 plus, with paretic motor symptoms of a year and a half's duration, and mental signs of a few weeks' duration was treated in April 1944 with 1.2 million units of penicillin, with improvement for 2 months, then relapse. A second course exaggerated his symptoms and he died in 3 weeks (September 1944) of bronchopneumonia and massive pulmonary embolus. There was a typical luetic mesaortitis. The brain, examined by Dr. Helena Riggs, showed cerebral arteriosclerosis of large and small vessels, meningeal opacity with small localized collections of lymphocytes and some occasional perivascular lymphocytes. The cortical architecture showed patchy cell loss in layers 2, 3, and 4 in frontal and parietal lobes and Ammon's horn. There was also extensive cell loss in putamen, pallidum, midbrain, hypothalamus, olive, and vagal nuclei. Few rod cells were seen and not much proliferation of fibrous astrocytes.

Dr. Riggs interpreted the findings as the result of anoxia, arteriosclerosis, and meningeal syphilis, rather than paresis. In fact, she considered the meager lymphocytic reaction the only sign of syphilis.

Case 3 (No. 1094).—A white male of 56 complained of convulsions of 3 years' duration, tabetic pains and ataxia of a year and a half's duration, and mental symptoms. The last consisted of a "nervous breakdown" 2 years before which lasted 4 months, and a recent inability to concentrate, memory loss, and depression. There was no gross psychosis although he was dull, confused, depressed and tremulous, but not disoriented. He showed the typical signs of early taboparesis, with Argyll-Robertson pupils.

Treatment in April 1947 with 9.6 million units of penicillin G resulted in a distinct amelioration of mental symptoms but the pains were unaffected. He had no more fits until December 1944, when he convulsed on the right side and died with a massive cerebral hemorrhage.

Blood and spinal fluid examinations are listed in table 2.

Necropsy: The brain was swollen and the gyri flattened. The subarachnoid space was covered with hemorrhage. On section of the brain it was apparent that the hemorrhage arose in the right internal capsule and had ruptured into the ventricle.

Table 2.—***Results of blood and spinal fluid examinations, case 3 (No. 1094)***

Date	Cells	Protein	Kolmer	Mastic
1947				
April	92	100	4444	3455555410
July	12	50	4444	5555554100
October	RBC	30	4444	3555420000

Microscopically, outside the hemorrhagic regions, areas of fairly normal cortex adjoined parts devoid of nerve cells; elsewhere, single layers, chiefly the third, were lost (fig. 1). Capillary proliferation and rod-cell formation

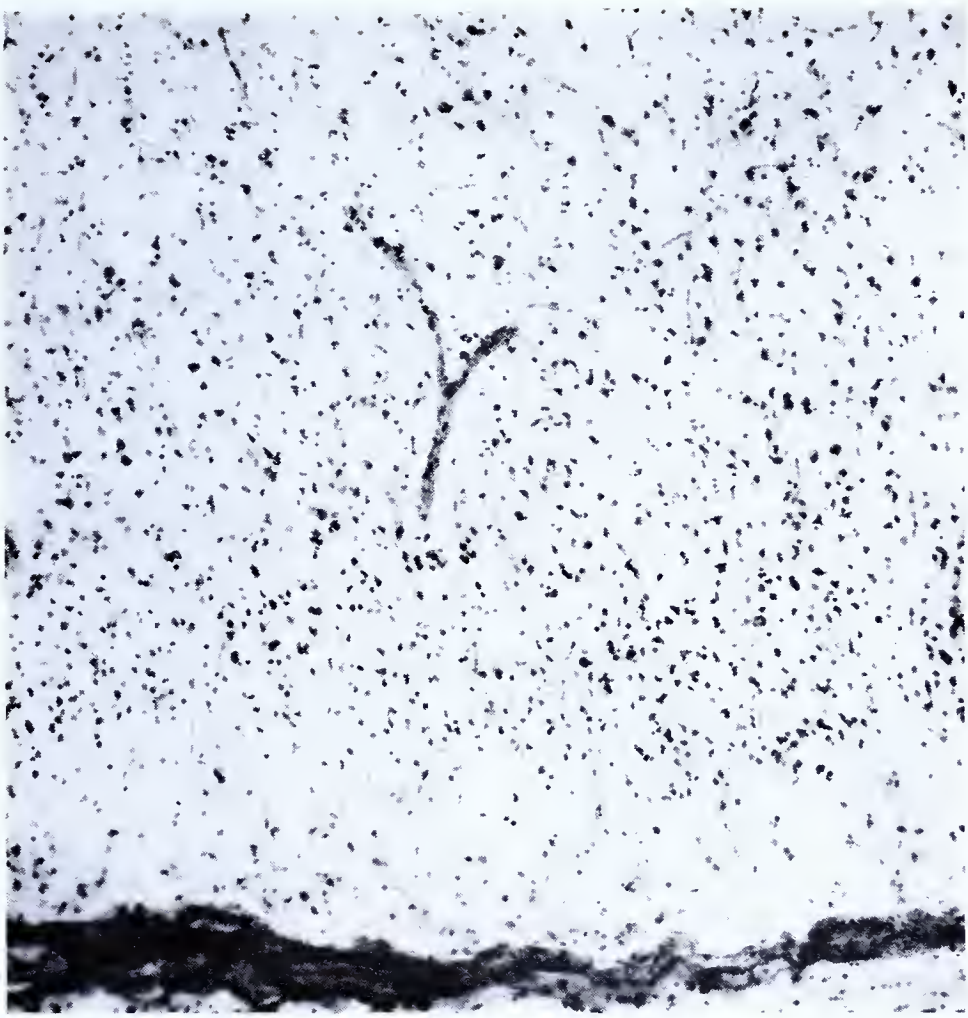


FIGURE 1.—Case No. 1094. Hand E stain. Frontal lobe. Loss of normal cortical architecture without evidence of inflammation or lymphocytic infiltration.

(Face p. 98)

FIGURE 2.—Case No. 227. Myelin stain. Demyelinization of posterior columns without infiltration or thickening of the meninges or blood vessels.

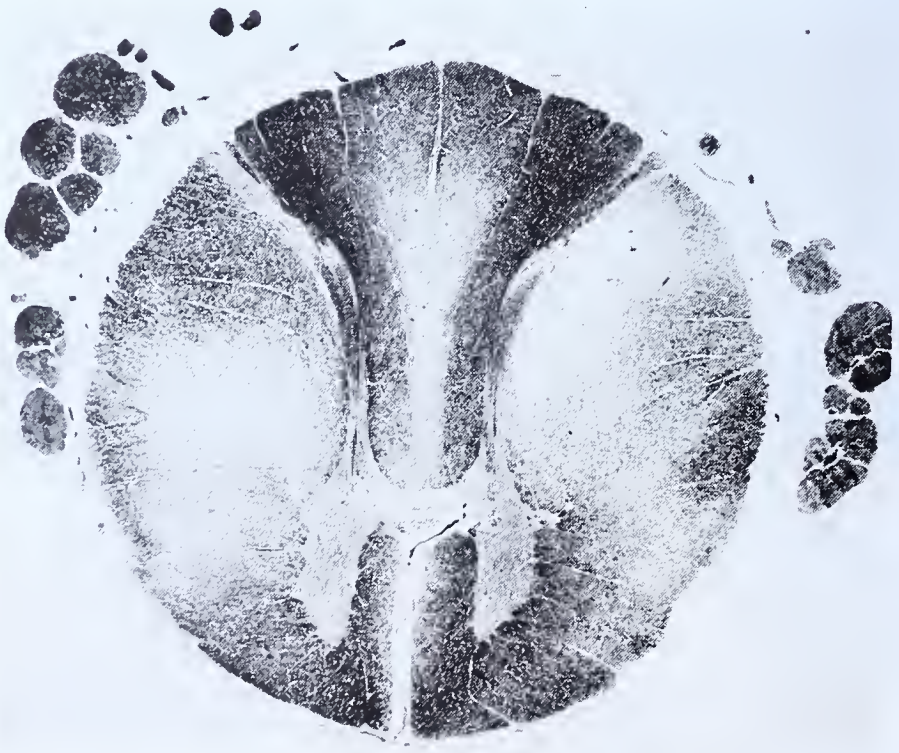


FIGURE 3.—Case No. 468. Myelin stain. Spinal cord. Demyelinization of all tracts in multiple sclerosis.

(Face p. 99)

were very marked. The blood vessels showed only minimal infiltration by occasional plasma cells. The meninges were thickened but there was only a very scanty lymphocytic infiltration. The whole appearance was that of a paretic cortex cleared of acute inflammatory signs. It resembled that of paresis successfully treated by malaria. The cord was not removed.

Of the three paretics, one dying 3 weeks after treatment showed the appearance of active paresis. The other two, dying at 5 months, had typical cell loss but relatively little of the lymphocytic infiltration which is usually encountered.

Meningovascular Syphilis

Case 1 (No. 86).—A white male of 65 had had perianal sores and gonorrhea at 17 without luetic therapy. His wife produced two healthy children and never had a miscarriage. He had the signs of hypertensive cardiovascular disease with minimal decompensation. He had an ataxic gait and absent vibratory sense to the iliac crests. The tendon reflexes were hyperactive. The pupils were normal. The STS was positive. Spinal fluid was type 3.

He died June 1947 of acute myelogenous leukemia, 5 months after treatment with 4.0 million units penicillin.

Necropsy: The aorta showed minimal atherosclerosis with no evidence of syphilis. The spleen was large (680 gm.) and soft and showed loss of normal architecture. All groups of lymph nodes were moderately enlarged. The nodes were soft and discrete and cut surface showed a homogeneous pinkish-gray appearance and the typical histological picture of myelogenous leukemia. The brain weighed 1,580 gm. and was grossly normal. Histologically the meninges were clear of inflammatory reaction and the cortical architecture well preserved. The blood vessels showed moderate arteriosclerotic change but no round cell infiltration.

The spinal cord had a few areas of degeneration which were not typical of tabes. There were a few areas of leukemic infiltration but nothing reminiscent of syphilis. Results of spinal fluid examination are listed in table 3.

Table 3.—*Results of spinal fluid examination, case 1 (No. 86)*

Date	Cells	Protein	Kolmer	Mastic
1944				
May	63	75	4 4 4 4	5555542100
June		1.2 million units penicillin		
1945				
January	RBC	100	4 4 4 4	3455554200
February		4.0 million units penicillin		
April	7	75	4 4 4 4	4442210000
1946				
May	RBC	40	0 0 0 0	1110000000
1947				
May	4	20	0 0 0 0	1110000000

Tabes

Case 1 (No. 131).—An elderly man with "burned out" tabes of 42 years' duration died as a result of an unsuspected auditory neuroma 6 months after treatment with 1.2 million units penicillin. The cord showed demyelinization of the posterior columns without inflammation.

Case 2 (No. 227).—A 56-year-old white male with tabetic ataxia of 8 years' duration, had been extensively treated since 1937 with malaria, bismuth, and arsenic. He showed in September 1944 typical ataxia, absent reflexes, Argyll-Robertson pupils, and absent vibration and position sense in the lower extremities. Despite three courses of penicillin (September 1944, 1.2; September 1945, 3.4; May 1946, 4.8) his ataxia increased.

He developed hypertensive cardiovascular coronary disease with decompensation and died February 20, 1948, of a bronchogenic carcinoma.

Blood serology was continually positive. The spinal fluid showed 2 cells, 20 mg. protein, Kolmer 112, and mastic 2221100000 before treatment but was thereafter negative on four examinations.

Necropsy: The heart was greatly hypertrophied. The aorta showed only a normal amount of atherosclerosis. The lungs showed a bronchogenic carcinoma which involved the visceral pleura and with lymphatic spread to the regional lymph nodes.

The brain weighed 1,350 grams. The convolutions were flattened but there was no gross atrophy of the frontal lobes. The pia arachnoid showed several small areas of grayish-yellow thickening, seen at the vertex and at the base which appeared to be related to the superficial vessels. Two or three tiny cystic hemorrhagic areas were seen in the region of the right caudate nucleus and putamen. The midbrain was normal.

Histologically there was a moderate degree of tabetic involvement of the spinal cord with slight thickening of the pia arachnoid. Neither the meninges nor the blood vessels shows infiltration (fig. 2).

The cortex was by and large normal with well-preserved architecture throughout, and no infiltration of meninges or vessels was seen.

Neither of these two tabetics showed the inflammatory reactions of tabes, although a typical posterior column degeneration was found. In view of the duration of the disease, the extensive therapy and the "inactive fluid" of case 2, it is possible that the process was "burned out," despite the progression of symptoms and signs. We have no reason here to assume that penicillin cleared up cell infiltrations.

Discussion

In the case just discussed the impressive finding is the near absence of the inflammatory infiltration usually encountered in luetic infection. In fact, the lack of the characteristic inflammation might cast doubt on the diagnosis of neurosyphilis in some cases, were it not for the presence of typical degenerative changes of the disease.

In two paretics and one meningovascular case the signs of "activity" in the spinal fluid diminished or disappeared under

therapy. In these it seems justified to assume that the lack of inflammatory reaction of meninges and brain was also the result of therapy, despite the fact that no histologic controls were available. We therefore adopt the tentative conclusion that penicillin was responsible for clearing the tissue of inflammatory signs.

In the case of the paretic who died 3 weeks after treatment, the infiltration was still present. This perhaps can be considered the result of insufficient time as well as of ineffectual therapy.

Miscellaneous Cases

Neurosyphilis and Associated Disease

Case 1 (No. 77).—A 34-year-old white female had a long history of rheumatoid arthritis and anemia with extensive chemotherapy, including gold. In 1938 a positive STS was discovered for which she received antiluetic therapy for one year.

In January 1944 she suddenly went blind in one eye because of optic neuritis with papillitis, and at this time received her first penicillin therapy. Vision partially returned within 4 months. She became blind in the other eye, this time without change in the disc. Another course of penicillin was followed by incomplete recovery of vision.

Three months after the last penicillin she developed giant urticaria for the first time in her life. Within a few days she developed signs of a lesion of the medulla, and died of respiratory failure. Blood STS was positive, Klein 128 units.

Diagnosis of this case was considered to be meningovascular syphilis plus optic neuritis of unknown cause, possibly luetic. The hives appearing 3 months after treatment were considered a form of penicillin allergy and the medullary lesion the result of a "hive" in the medulla. Alternative considerations were neuromyelitis optica and periarteritis nodosa.

Table 4.—*Results of spinal fluid examination, case 1 (No. 77)*

Date	Cells	Protein	Kolmer	Mastic
1941				
April	0	25	0 0 0 0	0000000000
1944				
March	15	40	4 4 4 4	4555542000
	3.0 million units penicillin			
June	5	10	0 1 1 2	2221100000
July	10	?	1 2 4 4	1122210000
	1.5 million units penicillin units; 4 typhoid fevers (104°F.)			
September	0	10	0 0 0 0	1110000000

Autopsy showed the presence of a demyelinating process affecting optic nerves, the posterior and lateral columns of the cord and an acute lesion in the medulla with neurosis and infiltrations with polymorphonuclear cells.

The cerebral cortex showed no cell loss. There was a mild infiltration of the vessels of the white matter. Punctate hemorrhages were seen in the brain and cord. There was no evidence of periarteritis nodosa.

The whole process had the appearance of a demyelinating disease without any evidence of the usual luetic involvement.

Acute Multiple Sclerosis with Positive Spinal Fluid—No Evidence of Syphilis

Case 1 (No. 468).—This 16-year-old white male developed diplopia and blurred vision in September 1944. These developed after an auto accident, which was unrelated as he was not injured and did not lose consciousness. This cleared after several months and he was well until February 1945 when he began to notice progressive difficulty in moving and coordinating his feet. In March he developed some dysuria, nocturia, and bedwetting.

On examination a mild euphoria was apparent. He walked on a wide base and his gait was grossly ataxic. His muscular tone was increased in the upper and more in the lower extremities. Abdominal and cremasteric reflexes were absent. There was a terminal tremor in the finger to nose test and ataxia on the heel-to-shin test. The tendon reflexes were increased with bilateral ankle clonus and a positive Babinski on the right. There were no sensory changes for vibration, position, pin prick, temperature, and touch.

His pupils were unequal and reacted poorly to light but well on convergence. A well-marked nystagmus on lateral and upward gaze was noted. Speech was slurred and staccato. The visual field of the left eye was constricted and showed a central scotoma. The general physical examination was normal. The teeth and skeletal systems showed no evidence of congenital syphilis. Slit-lamp examination showed no interstitial keratitis.

His blood serology was always negative. His spinal fluid examinations are listed in table 5.

Table 5.—*Results of spinal fluid examination, case 1 (No. 468)*

Date	Cells	Protein	Kolmer	Mastic
1945				
April 17	12	50	4 4 4 4	3455521100
August 11	10	40	4 4 4 4	4555421100
October 24	2	100	4 4 4 4	4555431000
1946				
January 30	8	75	4 4 4 4	2355541100

There was no history of venereal disease and no evidence of syphilis in the parents or two siblings. The mother had had no miscarriages. All members had negative serology. A maternal aunt was treated for lues.

He was given 4.8 million units of penicillin in 8 days by injection every 3 hours and then discharged. While at home his condition became progressively worse. By July 1945 he was unable to walk. Upper extremities became weak and the tremor worse. He was readmitted in August for further treatment. Physical examination confirmed above progression of symptoms.

At this time biologic false positive tests by Dr. Fred Boerner were reported as follows:

Blood: Flocculation units ½; fixation of complement units ¾; heterophile antibody (Davidsohn technic 1:14); class 2; group 1.

C.S.F.: Flocculation units 0; fixation of complement units ¾; class 1; group 1.

C.S.F. (one month later): Flocculation units 0; fixation of complement units ¼; class 2; group 1.

He was given 4.8 million units of penicillin in 16 days and in addition 25,000 units intrathecally every other day for eight doses. While in the hospital he developed bowel and bladder incontinence.

On October 24, 1945, further progression was apparent. He had marked

bowel and bladder sphincter disturbances. He was unable to walk. The upper extremities showed a marked tremor both at rest and on intent. His head, trunk, and legs had developed a marked tremor. All tendon reflexes were hyperactive and he showed bilateral patellar and ankle clonus. His optic discs showed some atrophy. The remainder of the examination was unchanged. He was last seen on February 5, 1946. He had become much worse. There was complete incontinence and large decubitus ulcers. All previous signs were exaggerated. Patient died at home on February 22, 1946.

Necropsy: Necropsy was performed in his home town. The dura mater was attached at the vertex and appeared normal. The longitudinal sinus showed post-mortem clot.

The brain was firm and normal in contour. There was some congestion of the vessels on the surface of the brain. The arachnoid was clear and did not seem to be thickened. The base of the brain showed no abnormality. There was mild cerebellar tonsillar herniation.

Cut sections of the brain showed very little to be considered abnormal. The lateral ventricles were moderately enlarged.

A portion of the spine grossly revealed no abnormality.

Microscopic examination: The spinal cord was the site of widespread foci of demyelination (fig. 3). Only the posterior columns remained myelinated. In the demyelinated areas the glia cells were increased in number and size and many showed four or more nuclei. There was little infiltration. In the pons there was a similar but much less widespread process. There was a moderate degree of lymphocytic infiltration. The cortex was well preserved and showed little demyelination.

Summary: The brunt of the process fell clearly below the medulla. There was not the slightest indication of lues. The meninges and blood vessels were not thickened or infiltrated. The picture was one of demyelination of the type of multiple sclerosis or related processes.

The patient had no history of syphilis nor treatment, therefore, a negative blood test, and positive spinal fluid in the presence of a neural disease is clearly not luetic. We have encountered others in this series with a similar syndrome of which the following may be an example.

Case 2 (No. 1134).—A 49-year-old Negro male with hypertension of at least 2 years' duration. No history of syphilis or treatment thereof. In 1944 he had a 10 day episode of confusion and agitation. Blood and spinal fluid at Philadelphia General Hospital were negative. No signs of neurosyphilis were uncovered then nor 2 years later when we saw him, 6 months after a stroke. STS repeatedly negative (table 6).

He died in coma in October 1947. Autopsy showed no evidence of luetic aortitis. The brain was grossly normal. There was a very extensive calcification and fibrosis of all cerebral vessels with great thickening of the intima. No infiltration of meninges or vessels was observed.

There is no evidence that this patient ever had syphilis except for the positive spinal fluids. The question of a nonspecific reaction must be considered.

Table 6.—*Results of spinal fluid examination, case 2 (No. 1134)*

Date	Cells	Protein	Kolmer	Mastic
1947				
June	8	75	4444	4555543100
June	9.6 million units penicillin			
October	0	150	0000	2443210000

Summary

Autopsy study of nine cases is reported. Two cases are considered neural disease with a positive spinal fluid but without syphilis. The diagnosis of one was acute multiple sclerosis, the other hypertensive cerebral vascular disease.

In the cases of syphilis one paretic dying 3 weeks after treatment showed the usual histology of the disease. In two others the inflammatory lesions were minimal. Also in one meningovascular and two tabetic cases there was little inflammatory reaction.

The evidence suggests that penicillin had cleared the infection.

Cerebral Blood Flow and Oxygen Consumption in Neurosyphilis [1]

John L. Patterson, Jr., Albert Heyman, and Fenwick T. Nichols, Jr.

The circulation and oxygen consumption of the brain have been found to be markedly altered in a group of patients with neurosyphilis. These studies, summarized in this report, have been made possible by the recent development by Kety and Schmidt (*1*) of the nitrous oxide technic for determining the cerebral blood flow in man. This method is based on the Fick principle, which states in brief that the amount of a given substance taken from or released into the blood stream by an organ is equal to the product of the blood flow through that organ and the arteriovenous difference of the substance. If the quantity of the substance absorbed or released and its arteriovenous difference can be measured, the blood flow can be calculated.

In the nitrous oxide method, a subanesthetic concentration of this gas (15 percent) together with atmospheric concentration of oxygen (21 percent) is inhaled. Serial samples of femoral arterial and internal jugular venous blood are obtained and analyzed for nitrous oxide content. Figure 1 shows representative curves for arterial and venous nitrous oxide concentrations obtained over a period of 10 minutes. At the end of this time equilibrium has been established between the brain and the jugular venous blood with respect to the nitrous oxide content. The quan-

[1] From the Departments of Physiology and Medicine, Emory University School of Medicine, Atlanta, Ga.

tity of the gas absorbed per unit weight of brain can therefore be obtained from the 10-minute venous concentration and the blood-brain partition coefficient for nitrous oxide. This coefficient is the ratio between the solubility of nitrous oxide per gram of brain and the solubility per milliliter of blood, and has been found to be unity. The solubility of this gas in the paretic brain has been found to be the same as in the normal brain (*2*). The dissimilarity in the average arteriovenous difference in the two pairs of curves should be noted. This method has been validated by comparative studies with more direct methods in monkeys (*1*). The oxygen consumption of the brain can be calculated from the cerebral blood flow and the arteriovenous difference.

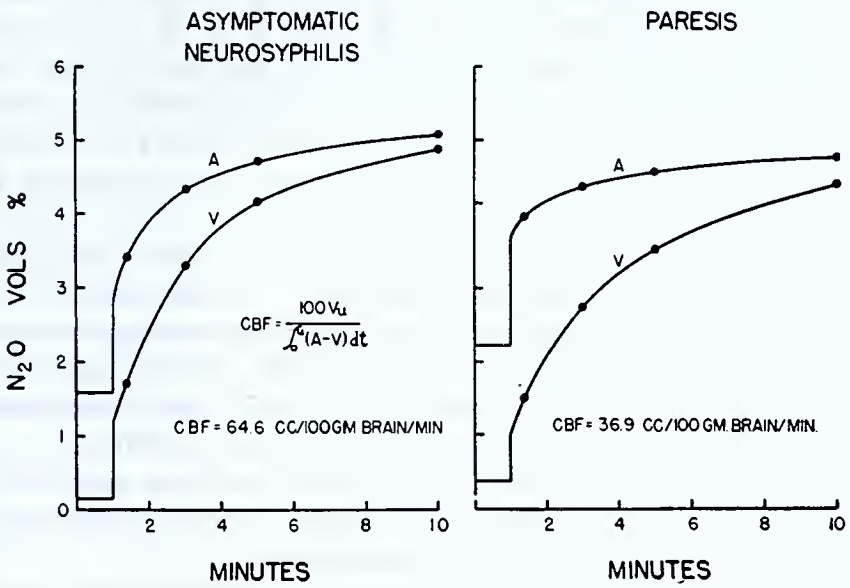


FIGURE 1.—Representative arterial and venous nitrous oxide curves. The cerebral blood flow (CBF) is obtained from the venous nitrous oxide concentration at 10 minutes (Vu) and the area between the arterial and venous curves ($\int_0^u (A-V)dt$). A CBF of 64.6 cc./100 gm./minute is in the high normal range, while a value of 36.9 is abnormally low.

A group of 61 patients with various types of neurosyphilis and 12 control subjects were studied by the above technic. All of the determinations were done before treatment. Twenty-six of the patients with neurosyphilis had paresis, 10 had meningovascular syphilis, and 25 had asymptomatic neurosyphilis of 2 to 28 years' duration. All of the patients with neurosyphilis had strongly positive spinal fluids. Most of the patients with meningovascular syphilis were studied within a few days after their vascular episodes.

The average cerebral blood flow in the 12 control subjects was

55.6 cc. per 100 gm. of brain per minute. The cerebral oxygen consumption was 3.17 cc. per 100 gm. of brain per minute. These figures agree closely with the values obtained by Kety and Schmidt for normal individuals: cerebral blood flow, 54 cc./100 gm./minute; oxygen consumption, 3.33 cc./100 gm./minute.

In the patients with paresis the average cerebral blood flow was found to be 41.6 cc./100 gm./minute or 75 percent of the value in the control subjects. Three of the patients had flows as low as 50 percent of normal, and only two patients had cerebral blood flows greater than the normal mean. The patients with meningovascular syphilis showed a reduction in cerebral blood flow comparable to that found in paresis. The average cerebral blood flow in patients with asymptomatic neurosyphilis, however, was almost identical with that obtained in the control group. Of possible significance is the fact that 9 of the 13 patients with asymptomatic neurosyphilis of more than 10 years' duration were in the group with the lowest blood flows. Since all of the patients had strongly positive spinal fluids, it was not possible to correlate the magnitude of the cerebral blood flow with the degree of the spinal fluid abnormality.

The cerebral oxygen consumption in most patients was altered in the same direction as the blood flow. In the patients with paresis, however, the reduction in oxygen consumption was usually greater than the reduction in cerebral flow. In this group, the average oxygen consumption was 2.25 cc., or 71 percent of normal. Several of these patients had cerebral oxygen consumptions less than 40 percent of normal. There was usually a very definite correlation between the degree of mental deterioration and the reduction in the cerebral oxygen consumption.

In meningovascular syphilis the oxygen consumption was diminished (2.4 cc./100 gm. of brain per minute) but was slightly greater than the oxygen consumption in paresis. In asymptomatic neurosyphilis the oxygen consumption was nearly the same as in the control subjects.

The effects of penicillin and fever therapy were studied in 17 patients. Nine of the eleven patients with paresis were given malarial fever therapy combined with penicillin; two patients with paresis and six with meningovascular syphilis were given penicillin alone. Fever therapy consisted of 50 hours with temperature above 103° F., and the total dosage of penicillin was 4.8 million units. The cerebral studies were carried out before treatment, and from 1 to 6 months after completion of therapy.

In patients with paresis no consistent changes were found to have occurred in the cerebral blood flow (fig. 2). However, the

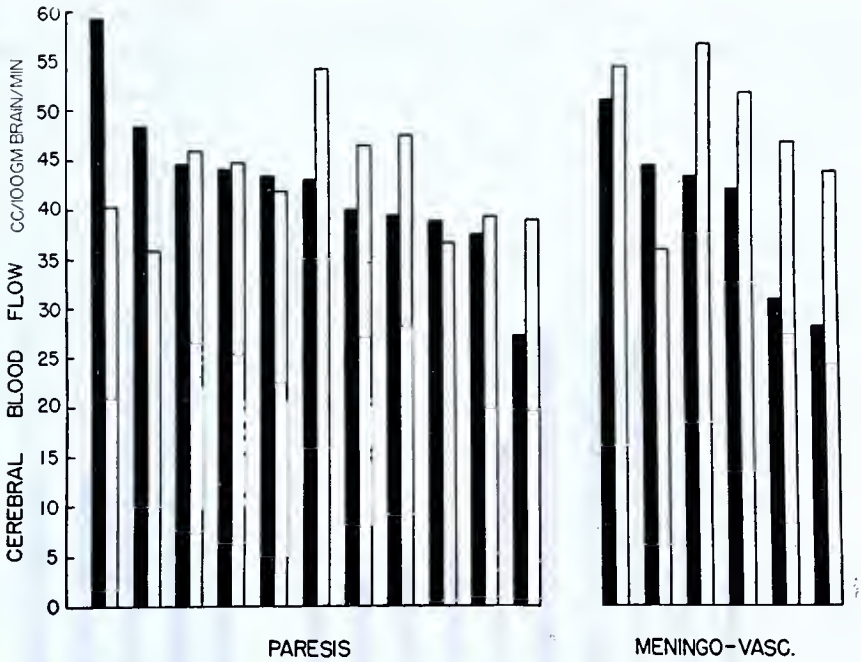


FIGURE 2.—The effect of treatment on the cerebral blood flow. The solid columns represent the pretreatment and the open columns the posttreatment determinations. It should be noted that practically all of the pretreatment values fall below the normal mean of 55.6 cc./100 gm./minute.

majority of patients with the lower initial flows showed an increase. In contrast, the cerebral blood flow was found to have increased to a significant degree following treatment in almost every patient with meningovascular syphilis. We were unable to establish a correlation between the increase in cerebral blood flow in these patients with improvement in the clinical manifestations. During the period of observation, most of the patients with hemiplegia or cranial nerve lesions continued to show the same degree of impairment of neurologic function as before treatment.

Cerebral oxygen consumption usually showed a marked rise following treatment in the patients with paresis (fig. 3), amounting to a mean increase of 35 percent over the pretreatment level. The improvement in the patient's mental status following treatment could be correlated to a great extent with the increase in cerebral oxygen consumption. The average oxygen consumption in patients with meningovascular syphilis increased slightly following treatment. Two patients with initially low values showed a marked increase.

The decreased cerebral blood flow in paresis and meningovascular syphilis is consistent with the pathologic changes known to occur in the cerebral vessels in these conditions. Rosenbaum et al. (*3*) have previously reported a diminution in total intra-

cranial blood flow in severely demented patients with paresis. The method used by these workers is now believed to give abnormally low values.

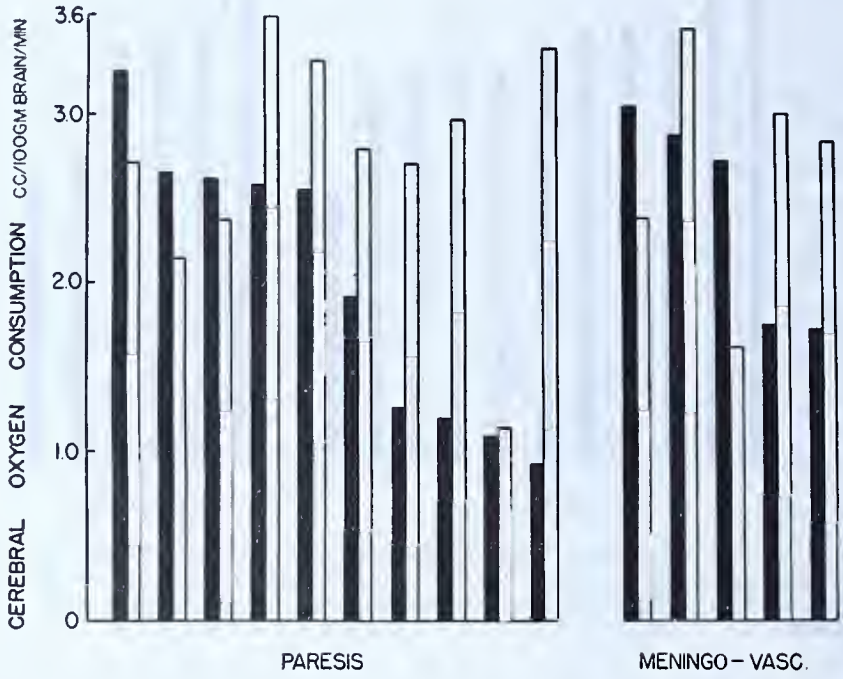


FIGURE 3.—The effect of treatment on the cerebral oxygen consumption. The solid columns represent the pretreatment and the open columns the posttreatment determinations. It should be noted that practically all of the pretreatment values fall below the normal mean of 3.17 cc./100 gm./minute.

The improvement in blood flow which often follows therapy of neurosyphilis suggests that either the structural vascular changes are to some extent reversible or that treatment alters the vasomotor control of the cerebral circulation.

In addition to the diminution in cerebral blood flow, many of the patients with paresis showed a decrease in the arteriovenous oxygen difference. Himwich, Wortis and others (*4*, *5*) have reported similar findings. Himwich concluded that the brain in paresis fails to utilize available oxygen. The alterations in the cerebral blood flow and oxygen consumption are often of different magnitude and following treatment are occasionally found to have changed in opposite directions. These facts suggest that syphilis affects the brain by a direct action on cellular metabolism in addition to reducing its blood supply. Other possible explanations for the decreased oxygen consumption of the brain in neurosyphilis are that the destroyed neurons are replaced by glial tissue having a lower metabolic activity or that there exists a barrier to diffusion of oxygen from the vessels to the nerve cells.

References

1. KETY, S. S.; SCHMIDT, C. F.: The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. J. Clin. Invest., 27: 476, 1948.
2. KETY, S. S.; HARMEL, M. H.; BROOMELL, H. T.; RHODE, C. B.: The solubility of nitrous oxide in brain and blood. J. Biol. Chem., 173: 487, 1948.
3. ROSENBAUM, M.; ROSEMAN, E.; ARING, C. D.; FERRIS, E. B., JR.: Intracranial blood flow in dementia paralytica, cerebral atrophy and schizophrenia. Arch. Neurol. & Psychiat., 47: 793, 1942.
4. HIMWICH, H. E.; FAZEKAS, J. E.: The oxygen content of cerebral blood in patients with acute symptomatic psychoses and acute destructive brain lesions. Am. J. Psychiat., 100: 648, 1943–1944.
5. WORTIS, J.; BOWMAN, K. M.; GOLDFARB, W.: Human brain metabolism. Normal values and values in certain clinical states. Am. J. Psychiat., 97: 552, 1940.

Early Diagnosis of Syphilitic Primary Optic Atrophy[1]

Joseph V. Klauder and George P. Meyer

In a previous communication (*1*) study of 397 patients with syphilitic primary optic atrophy was presented. The visual acuity of 61 percent of these patients when first seen was less than 6/60 in both or in the better eye (in 44 percent it was 1/60 to 6/60 and in 17 percent it was less than 1/60). This represented an unfortunate experience in early diagnosis of syphilitic optic atrophy among the ward and clinic patients at Wills Hospital.

Our purpose now is to discuss the earliest signs of syphilitic optic atrophy, prodromal symptoms, and pitfalls in early diagnosis.

Pertinent data in the study of our 397 patients in relation to early diagnosis are as follows: The occurrence of optic atrophy in patients whose early syphilis was untreated. The number of patients who had no knowledge of infection and no previous serologic tests for syphilis. The complaint of impaired visual acuity was frequently the first and only symptom that motivated medical consultation. The lack of ophthalmologic examination of such patients who consulted physicians or clinics in what was presumably the pre- or prodromal stages of subjective impaired visual

[1] From the Clinic for Treatment of Ocular Syphilis, Wills Hospital, Philadelphia, Pa. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Wills Hospital, and later under a grant-in-aid from the Research Grants and Fellowship Division, National Institutes of Health, U. S. Public Health Service.

acuity. Thirty-one percent of patients [2] at onset of visual loss consulted an optometrist for their initial treatment.

Syphilitic primary optic atrophy occurs in association with all forms of neurosyphilis, of acquired, and of congenital syphilis. From pathologic studies Bruetsch (*2, 3, 4, 5*) observed syphilitic optic atrophy occurring as a focal form of neurosyphilis without other pathologic evidence of neurosyphilis. Clinically, however, we have rarely observed optic atrophy in a syphilitic patient who had no neurologic abnormalities of neurosyphilis and whose spinal fluid was negative. The disease is seen more frequently in association with the tabetic or taboparetic form of neurosyphilis. Although Bruetsch (*3*) (later discussed), on the basis of anatomic investigation, has observed no great difference in its incidence in tabes and in general paresis.

The incidence of optic atrophy in patients with tabes of acquired syphilis is generally stated to be 10 to 15 percent. The interval between infection and onset of optic atrophy is rarely less than 10 years, the average is 18 years. The predominating age for patients with acquired syphilis is 40 to 50, and for congenital syphilis 15 to 25. Its incidence is greater in white patients than in Negroes (in our series 57 percent compared to 43 percent). The disease, however, is more frequent among neurosyphilitic Negroes of both sexes than among neurosyphilitic white patients (*6*). Males are more affected than females, a ratio varying, as reported by different investigators, from 3.5:5.5 to 3.5:1.

An important consideration in early diagnosis is the considerable percentage of our patients whose underlying neurosyphilis pursued, so far as concerned subjective symptoms, a silent course. As has been pointed out by others, optic atrophy associated with the tabetic form of neurosyphilis rarely occurs in what is called inferior or "leg" tabes in which there is present the triad of tabetic symptoms—lightning pains, dysuria, and ataxia. In our series of patients it was unusual to observe bladder disturbance, visceral crisis, arthropathy, headache, "nervousness," pain of radiculitis, and other subjective symptoms of diffuse meningovascular neurosyphilis, or paralysis of one or more of the oculomotor muscles.

In addition to complaint of impaired visual acuity the most frequent prodromal symptoms of optic atrophy were pain in the legs and diplopia. Pain in the legs was typical of the tabetic type—stabbing, lancinating—occurring and recurring in "crisis." It was usually not incapacitating and sleep disturbing. It antedated by long periods subjective visual loss and was in many

[2] These figures are those of Lehrfeld and Gross, Am. J. Ophth., 21:435, 1938. Study of syphilitic optic atrophy of patients attending Wills Hospital.

patients elicited only upon questioning the patient. This was true too of diplopia, which was usually transitory, and invariably preceded, frequently by years, complaint of visual loss.

Some patients, in addition to optic atrophy and positive spinal fluid, may have only pupillary changes as the only neurologic abnormality. Such cases have been designated as "optic tabes" and "preataxic optic atrophy," and illustrate how difficult it is accurately to classify the type of neurosyphilis associated with optic atrophy. The pupils, however, were hardly ever normal. The most constant findings in our series of patients, in addition to optic atrophy, were positive serologic tests for syphilis, positive spinal fluid, and pupillary abnormalities—inequality, irregularity, sluggishness in reaction to light, Argyll-Robertson pupil, or fixed to light and accommodation. As is well known, pupillary abnormalities are one of the earliest and most constant signs of neurosyphilis, preceding by years the appearance of subjective symptoms. They constitute a "short cut" in clinical examination to diagnosis of neurosyphilis. Determination of the state of the pupils is of great importance in examination of a syphilitic patient beyond the early stage of infection and should aid in early diagnosis of optic atrophy.

Pathology of Syphilitic Primary Optic Atrophy

Comprehensive reviews of this phase of optic atrophy have been published by Moore (*7*), Schiff-Wertheimer and L'Hermitte (*8*), and by Moore and Woods (*9*).

Moore and Woods concluded there is general agreement among pathologists that the process begins in the intracranial portion of the optic nerve distal to the chiasm. There is thickening and perivascular round cell infiltration of the overlying membranes, especially the pia, and of the connective tissue septa of the nerve and that degeneration occurs first in the marginal fibers of the nerve. There is, however, no agreement as to the important question of the relationship, if any, of the inflammatory changes in the membranes and septa to the degenerative process in the nerve, since the former are frequently found in neurosyphilitics who do not show the latter.

From pathologic studies Behr (*10*) envisages the disease as occurring in two forms: (1) an inflammatory form with secondary degeneration of the nerve fibers, and (2) primary degeneration in the form of tabetic atrophy of the optic nerves. Still others postulated a basilar meningitis form and a tabetic form of syphilitic optic atrophy.

Since Moore and Woods' (*9*) review (published in 1940) the most notable pathologic study of syphilitic optic atrophy has been made by Bruetsch (*2, 3, 4, 5*). The employment of modern methods of staining and their use in alternating serial sections permitted the simultaneous observation of both the inflammatory and the degenerative phase of syphilitic optic atrophy.

Apparently Bruetsch has more clearly visualized an inflammatory exudative phase preceding degenerative changes than any other investigator. According to Bruetsch the principal site of the inflammatory pathologic process is in the intracranial portion of the optic nerves or in the chiasm, or both, and is dependent on a varying degree of syphilitic basilar meningitis. The inflammatory lesion in the optic nerves and chiasm consists of cellular infiltrations in the septal connective tissue and around the blood vessels. As these exudative processes become extensive, demyelination (atrophy) of the nerve ensues, which in the majority of instances begins in the outer margins, where the syphilitic inflammation is most pronounced. He stated the opinion that visual field defects may be caused by exudative processes in the marginal zone before atrophy of the nerve fibers has taken place and that such defects may improve or disappear after antisyphilitic treatment. This is not to be expected, however, if degeneration was present at the time therapy was given.

He observed no difference in the pathologic process of optic atrophy in patients with taboparalysis in contrast to general paresis, indeed no great differences in the incidence of optic nerve involvement in the two diseases. His studies supported only the inflammatory pathogenesis of optic atrophy. He believes the clinical dictum of the greater frequency of optic atrophy among tabetics and taboparetics is more apparent than real and is in relation to diagnostic discrepancies in clinical classification of neurosyphilis, the failure of clinical recognition of the disease in general paralytics, and a shorter span of life. The question why only a certain number of patients with neurosyphilis develop optic atrophy, he explains by the considerable variation as to the intensity of the pathologic processes in different regions of the brain and its meninges, the optic chiasm, and the meninges of structures adjacent to the chiasm.

Early Ophthalmologic Diagnosis

The following changes have been reported by different writers as the earliest evidence of syphilitic optic atrophy: Loss of dark adaptation. Visual field defect preceding loss of central vision

and pallor of the optic nerve. Such field defect may comprise a central or cecocentral scotoma, enlargement of the blind spot or contraction of the peripheral visual fields. Loss of the field for color, particularly red and green. Pallor of the optic disc.

The older ophthalmologists, notably Behr (*10*, *11*), emphasized loss of dark adaptation as an early symptom. We know of no study of loss of dark adaptation as determined by modern methods. We have had no experience of patients with early syphilitic optic atrophy. In any event such method as a means of early diagnosis we do not regard as practical.

Igersheimer (*12*), Fuchs (*13*), Paton (*14*), and Sloan and Woods (*15*) reported a variety of field defects (such as are shown in figs. 1 to 8) occurring in the absence of pallor of the discs and loss of central vision. Fuchs (*13*) stated the opinion that a central scotoma may first be demonstrated only for red and green.

Demonstration of scotoma, enlargement of the blind spot, and loss of function for color as early evidence of optic atrophy necessitates making tangent screen and perimetric studies with white, red, green, blue, and yellow with several-sized test objects on each color in order to secure a quantitatively accurate picture. The desirability of such procedure cannot be questioned but the practicability and reliability of results with some patients can be questioned. Such studies require time (1 to 2 hours) and patience of a skilled operator, preferably an ophthalmologist. Moreover, the average patient, particularly the clinic type, has neither the patience nor the discriminatory acumen necessary for accurate quantitative decisions. Some ophthalmologists are of the opinion that perimetric studies with small (1- and 3-mm.) white test objects will elicit very early functional loss comparable to quantitative studies with color test objects. Such procedure is more practical, less time-consuming and more satisfactory in examination of clinic patients. That has been our experience.

The opinion has been stated by some that pallor of the disc precedes visual field defects and impairment of central vision, and instances of this have been reported. Apparently such occurrence is considerably less common than visual field defects as an initial symptom of optic atrophy.

Kestenbaum (*16*) and others emphasize loss of capillarity of the optic discs as diagnostic evidence of optic atrophy. In our experience this symptom occurs too late to have any consideration in early diagnosis of the disease.

Cases 1, 2 and 3 (figs. 1 to 8) are patients with neurosyphilis who had on repeated examination variable degrees of constriction of the visual field for form and color. The central visual acuity

and the optic discs were normal in two of the three patients. Following treatment (with penicillin and, in addition in two patients, with induced malaria) the visual field defects disappeared. We never observed this following treatment of patients with syphilitic optic atrophy if the optic discs were pathologically pale at onset of treatment.

In accordance with the studies of Bruetsch (*2, 3, 4, 5*) the pathologic involvement of the optic nerves of our patients were in the inflammatory or preatrophic stage of optic atrophy and were amenable to antisyphilitic therapy in contrast to the atrophic stage in which the changes are irreversible and the goal of treatment is merely to retard or check the progress of the disease.

Further clinical studies are needed to determine how frequently field defect occurs as the only evidence of preatrophic changes in the optic nerve, and the effect upon it of antisyphilitic treatment, and how long it takes for central visual loss and pallor of the disc to occur in the treated and untreated cases. These questions are doubtless dependent upon the intensity and rate of progress of the pathologic process. The location of the lesion too will determine the character of the field defect: peripheral, central, or mixed.

The inflammatory processes of late syphilis are notoriously slow. The course of optic atrophy (in the atrophic stage) is variable, in some patients blindness ensues in one year or less from onset of subjective loss of visual acuity. On the other hand the disease, though untreated, may progress but slowly for years. This is illustrated in the case of a patient aged 62 years. He had syphilitic primary optic atrophy; with correction visual acuity was 5/60 in one eye and 6/30 in the other. He never received antisyphilitic treatment. He first noticed impaired vision 10 years prior and had diplopia 25 years prior. Behr (*10*) pertinently stated the opinion that the pathologic process of syphilitic optic atrophy exists for a long time prior to disturbance of visual acuity.

Apparently then there is an interval, at least in some patients (cases 1, 2 and 3), in the evolution of optic atrophy in which the diagnosis can be made in the inflammatory or preatrophic stage of the disease. Treatment in the inflammatory stage obviously affords better prognosis than in the atrophic stage.

It will be observed that in one of our patients (case 1) contraction of the visual fields was observed for 3 years without impairment of central visual acuity or pallor of the disc, although in this interval chemotherapy was administered. It will further be observed that in two patients (cases 1 and 2) chemotherapy alone did not suffice to cause disappearance of the contraction nor did (in case 1) the initially employed smaller total dose of penicillin.

Comment

If only to emphasize the possibility of early diagnosis of syphilitic primary optic atrophy by peripheral field defect as an initial and only symptom, the disease should be envisaged and taught as occurring as a two stage process.

It requires no clinical acumen to diagnose optic atrophy in a patient with neurosyphilis who has pale optic discs and visual field defects. Insofar as concerns a rapid course to blindness diagnosis in this stage is somewhat comparable to diagnosing malignant disease from cachexia.

It should be emphasized that in two of our patients (cases 1 and 2) the only motivation for perimetric study was the principle that in every patient with neurosyphilis such study is indicated. Only in this way can the disease be diagnosed early and opportunity afforded to combat syphilis as a cause of blindness.

To facilitate the early diagnosis of optic atrophy it is necessary that ophthalmologists and all physicians who examine patients with syphilis have a high degree of awareness of the optic nerve, to "reach out" for the diagnosis in the early or preatrophic stage of impending optic atrophy. In records of private, ward, and clinic patients too infrequently no mention is made of such examination unless the patient complains of visual loss or tryparsamide therapy is given.

In order to diagnose optic atrophy early, ophthalmologic and perimetric examinations should be made on all neurosyphilitics whether the blood or spinal fluid tests are positive or negative. Any physician can diagnose pupillary abnormalities. If found, spinal examinations should be made to exclude optic atrophy. Lack of ophthalmologic examination of syphilitic patients in the late stage of infection without evidence of neurosyphilis we do not believe would constitute an important error of omission.

Ophthalmologists are well situated to exclude optic atrophy of every patient examined with pupillary abnormalities. The industrial physician is likewise in a favorable position to expedite the diagnosis of early syphilitic optic atrophy, since he encounters in mass examination the type of person who develops the disease, one whose infection is unknown to the patient and remains untreated.

Facilities should be made for routine ophthalmologic examination of selected patients in clinics treating syphilis.

It is far better for the patient that his syphilitic infection be evaluated in relation to early stages of the devastating forms of the disease—cardiovascular syphilis, neurosyphilis and optic

atrophy—rather than in terms of positive or negative serologic tests.

The ophthalmoscope and perimeter are as essential as the spinal puncture needle in the diagnosis and management of syphilis and its complication, primary optic atrophy.

Case Records

Case 1

N.S. (3374), a white girl, aged 13 years, was first seen in December 1943. She was referred as a juvenile tabetic for ophthalmologic examination by a venereal disease clinic (Department of Health, Philadelphia). She had received 5 injections of an arsenical and 14 injections of a bismuth compound.

Both pupils were irregular, semidilated, stiff to light but reacted on accommodation. The biceps and triceps reflexes were hypoactive, the patellar and Achilles reflexes were absent. There were no symptoms suggestive of paresis. Visual acuity in the right eye was 6/6-2, in the left eye 6/6-3. The optic discs were normal in color, their margins well defined, no pathologic lesions in the fundi. The perimetric fields showed contraction for form and for color, and are shown in figure 1. The serologic tests for syphilis were strongly positive, the spinal fluid was positive in all phases, the gold sol curve was 0012234320.

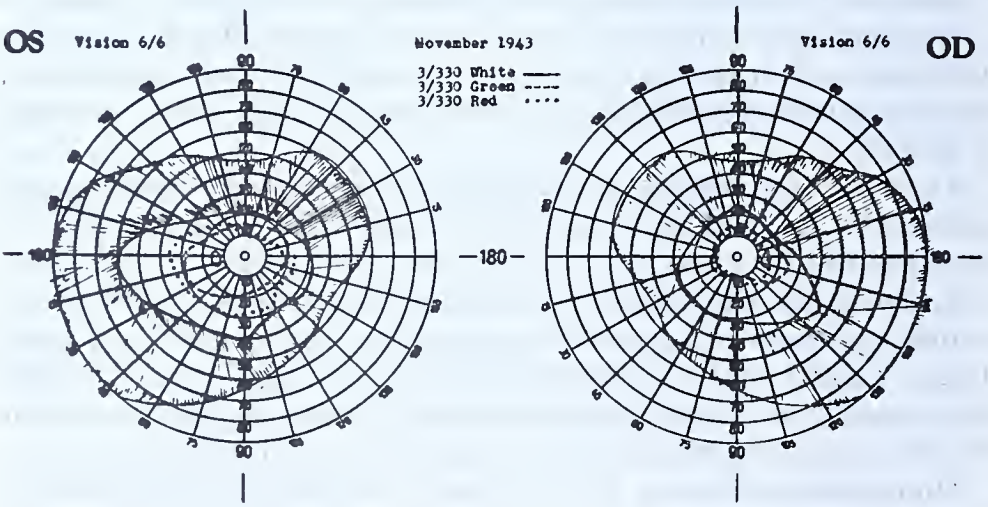


FIGURE 1 (case 1).—Showing contraction of visual fields for form and color at first examination, November 1943. Repeated examination showed the same result. The optic discs were normal in color.

From December 1943 to February 1946 treatment consisted of 24 injections of an arsenical and 30 injections of a bismuth compound. Repeated perimetric field studies showed persistent contraction. The fields taken January 1946 are shown in figure 2. The sodium salt of penicillin was administered in February 1946, injections were given every 3 hours for 7½ days for a total dose of 4,200,000 units. Chemotherapy was discontinued.

Early in 1946 symptoms suggestive of paresis appeared, she became difficult to manage at home and in school, uncooperative, at times sulky, independent,

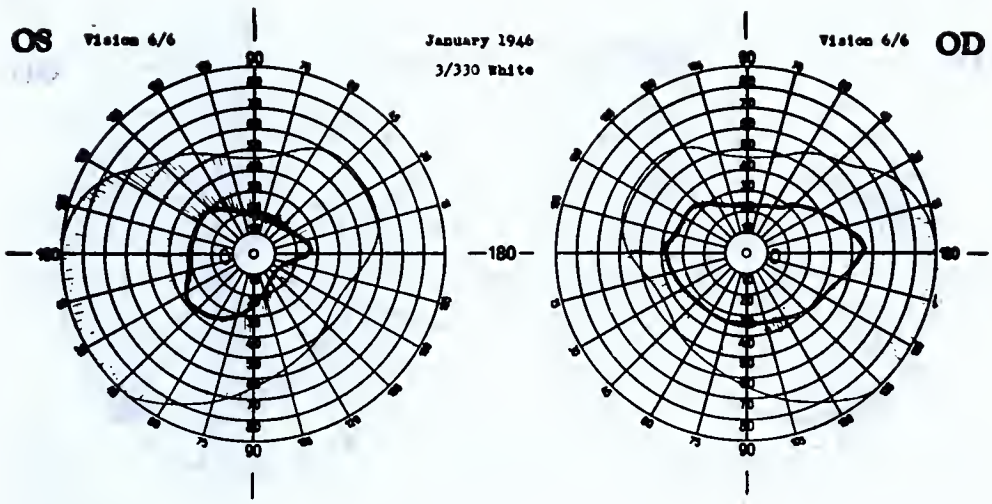


FIGURE 2 (case 1).—Showing continued contraction of visual field in January 1946. Up to this date treatment comprised only chemotherapy.

flippant and self-willed. There was impairment of attention and concentration, she was oriented and had no symptoms of psychosis. Neurologic signs remained unchanged except for some slurring of speech. The gold sol curve was now of the paretic type. In April 1947 malaria therapy was instituted (111 hours of fever over 100° F.) and 8,000,000 units of penicillin. Subsequent to this treatment symptoms of paresis gradually disappeared and no further treatment was given. The perimetric field of September 1947 showed considerably less contraction as shown in figure 3. Spinal fluid examination in May 1948 was normal except for positive Wassermann reaction only in the first two dilutions. Perimetric fields of March 1948, October 1948 (fig. 4), and March 1949 were normal. The optic discs remained normal in color. Central visual acuity remained unchanged since first admission.

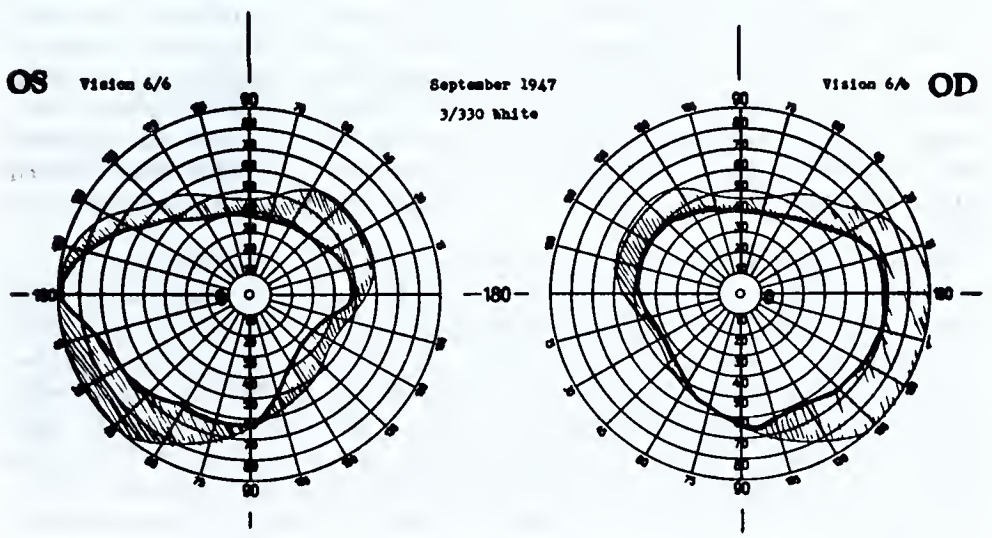


FIGURE 3 (case 1).—Showing improvement of visual fields in September 1947. In February 1946, 4,200,000 units of penicillin was administered and in April 1947 induced malaria and 8,000,000 units of penicillin.

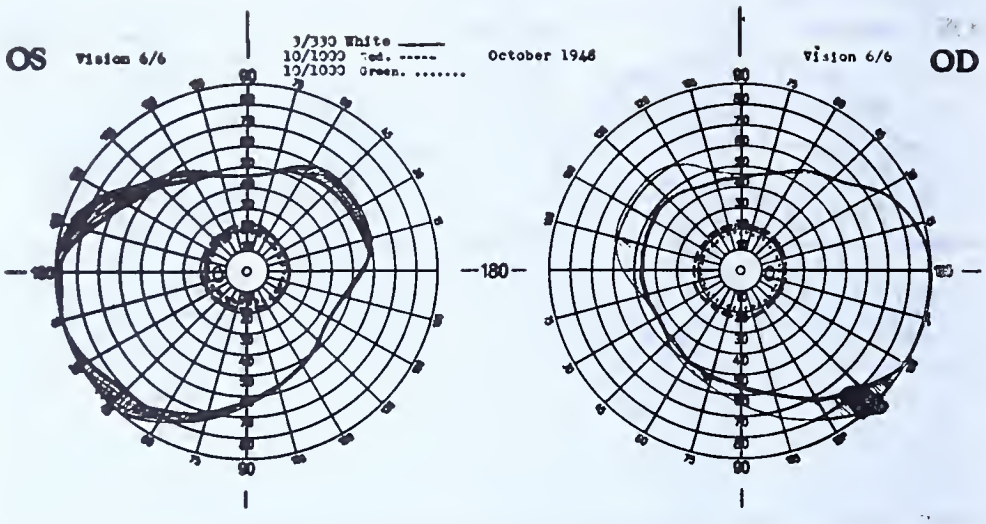


FIGURE 4 (case 1).—Showing normal visual fields for form and color in October 1948. Visual fields were also normal in March 1949. Central visual acuity and color of the optic discs remained normal.

Case 2

G.F., a white woman, aged 51 years, was first seen in May 1946.[3] On account of a positive Wassermann reaction she received injections in the arms and buttock at irregular intervals for "many years." She desired a change in her glasses; other than that, she had no complaint except occasional lancinating pains in the legs of several years' duration.

She presented neurologic abnormalities of tabes. Both optic nerves were normal in color. Visual acuity in the right eye without correction was 6/22, with correction 6/5-3; in the left eye without correction 6/22, with correction 6/5. The perimetric fields showed concentric contraction to form and color as shown in figure 5. Repeated examinations showed the same degree of contraction. The Wassermann and Kahn reactions were positive. The spinal fluid was negative in all phases. We were informed by the physician who treated her that treatment consisted of arsenical and bismuth; no tryparsamide was administered. About one year prior, one physician administered 100,000 units of penicillin given three times in one week, then weekly for 6 weeks.

In December 1946 the sodium salt of penicillin was administered every 3 hours for a total dose of 6,400,000 units given in 7½ days. She was not seen again until January 1949. She had gained in weight and had no complaint excepting pains in the legs which were less pronounced. She had been treated by several physicians. She had had daily injections of 300,000 units of penicillin in oil for 14 consecutive days and "many" injections of a bismuth compound. Her visual acuity with correction was the same as when first seen, the optic discs were normal in color, the perimetric fields were normal (fig. 6). The serologic tests for syphilis were less positive than on first admission.

[3] This patient is case 6 in our previous communication (*1*). Further observation is now reported.

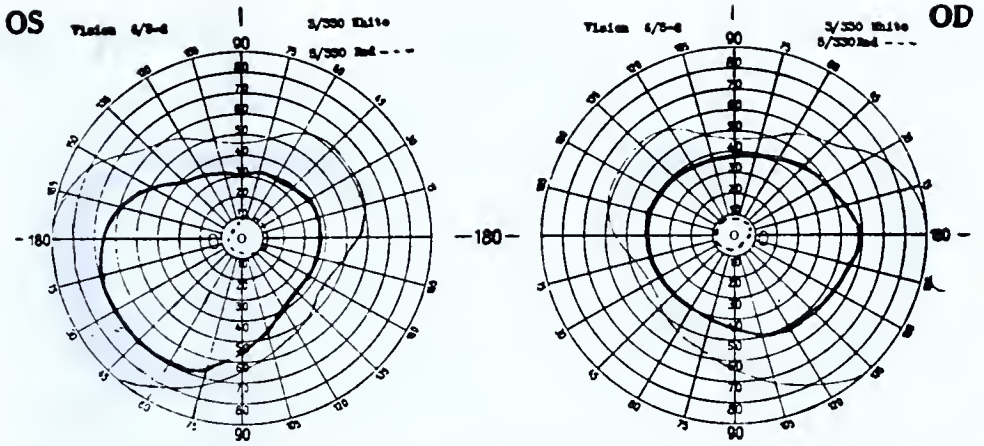


FIGURE 5 (case 2).—Showing contraction for form and color at first examination in May 1946. The optic discs were normal in color. The patient was a tabetic and had received only chemotherapy.

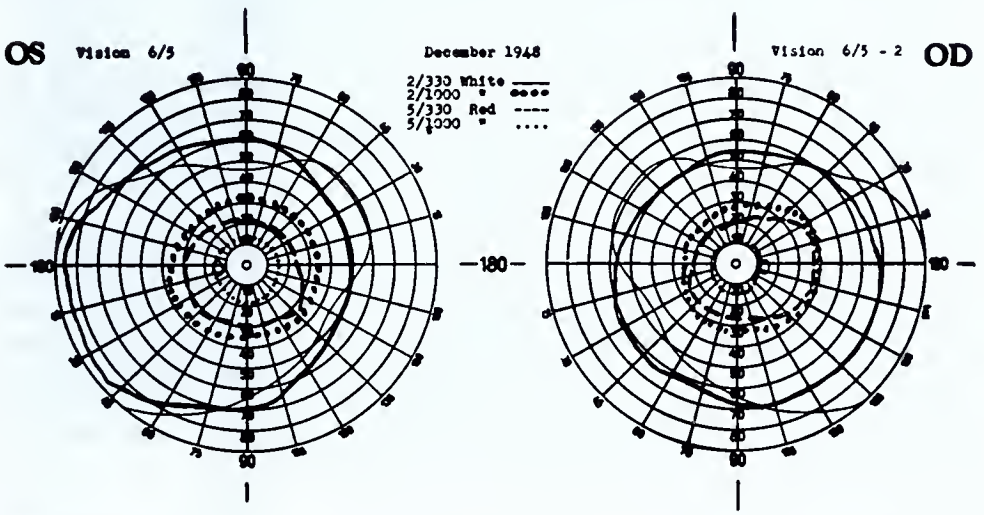


FIGURE 6 (case 2).—Showing normal visual fields in December 1948. Penicillin had been administered at two different times as well as chemotherapy.

Case 3

A.S. (L4103), a white woman, aged 52, was first seen in December 1947. Her chief complaint was impaired vision of the left eye of 8 months' duration appearing after a "nervous breakdown." At that time she had crying spells, impaired memory, and at times was confused. For the past 10 years she has had an occasional sharp pain in both legs.

Her station and gait were normal; motor power, coordination, and sensation were intact over the trunk and extremities. The patellar reflexes were hyperactive and unequal, the right Achilles reflex was absent, the left was diminished. There were pupillary abnormalities. The serologic tests for syphilis were strongly positive, the spinal fluid was positive only in some phases. Visual acuity in the right eye without correction was 6/20 plus 3, with correction 6/9; in the left eye without correction 2/60, with correction 3/60. The right optic disc was normal, the left was pale on the temporal

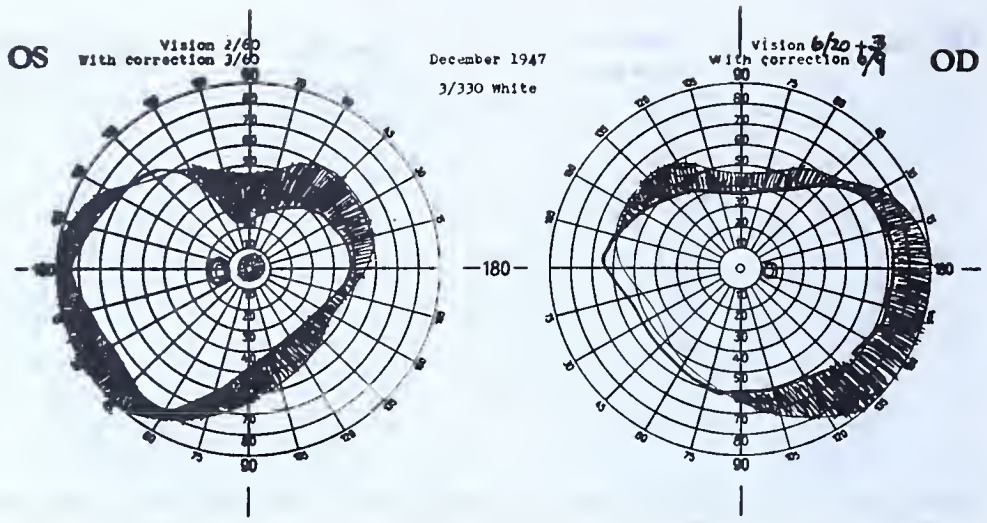


FIGURE 7 (case 3).—The patient had meningovascular neurosyphilis and complained of visual loss in the left eye of 8 months' duration. Only the left optic disc showed pallor of the temporal side. The figure records the degree of central visual loss and contraction of peripheral fields. The scotomas in both eyes are discussed in the case record.

side. The peripheral fields are shown in figure 7. The central screen of the right eye was normal except for a pericecal relative scotoma to 2/1,000 mm. white test object, the left eye showed a flat contraction of the upper field and a pericecal relative scotoma to 2/1,000 mm. white test object and a central scotoma to 2/1,000 mm. white test object.

In January 1948 she was treated with malaria and conjointly with 6,000,000 units of penicillin G administered in 8 days. Following this therapy there was a gradual disappearance of her "nervous" symptoms, she gained weight, and her emotional tone became normal. Repeated perimetric fields showed a gradual disappearance of the constriction and gradual improvement of visual acuity of the left eye. In March 1949 the peripheral fields were full (fig. 8), with correction visual acuity in the left eye was 6/15, in the right 6/9. There was still pallor of the temporal side of the left disc.

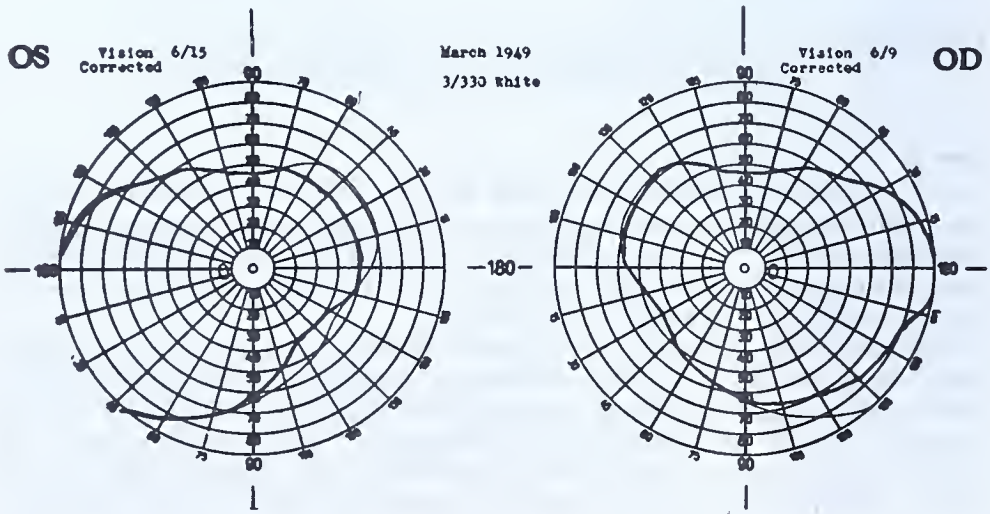


FIGURE 8 (case 3).—Showing normal peripheral fields for form and improvement of visual acuity of the left eye. Induced malaria and 6 million units of penicillin were administered in January 1948. Subjective symptoms of neurosyphilis disappeared.

References

1. Klauder, J. V.; Meyer, G. P.; Gross, B. A.: Syphilitic primary optic atrophy as a cause of blindness; importance of early diagnosis. Am. J. Syph. Gonor. & Ven. Dis., 32: 574–586, 1948.
2. Bruetsch, W. L.: Malaria therapy in syphilitic primary optic atrophy, J.A.M.A., 130: 14, 1946.
3. Bruetsch, W. L.: The frequency of syphilitic primary optic atrophy in general paralysis. A clinico-Anatomical study. Am. J. Psychiat., 104: 725–729, 1948.
4. Bruetsch, W. L.: Unilateral syphilitic primary optic atrophy. Arch. Ophth., 39: 80, 1948.
5. Bruetsch, W. L.: Surgical treatment of syphilitic primary optic atrophy of the optic nerves (syphilitic optochiasmatic arachnoiditis). Arch. Ophth., 38: 735, 1947.
6. Moore, J. E.; Hahn, R. D.; Woods, A. C.; Sloan, L.: The treatment of syphilitic primary optic atrophy. Am. J. Syph., Gonor. & Ven. Dis., 26: 407, 1942.
7. Moore, J. E.: The syphilitic optic atrophies, with especial reference to primary optic atrophy. Medicine, 11: 263, 1932.
8. Schiff-Wertheimer, S.; L'Hermitte, J.: Pathogenese et traitement de l'atrophie optique tabetique. Bull. Soc. d'Opht. de Paris, 44: 1–95, 1932.
9. Moore, J. E.; Woods, A. C.: The pathology and pathogenesis of syphilitic primary optic atrophy. Am. J. Ophth., 23: 1–40, 1940.
10. Behr, C.: Syphilis und Sehnerv. Med. Welt., 12: 1515, 1938.
11. Das Verhalten und die diagnostische Bedeutung der Dunkeladapation bei der verschiedenen Erkrankungen des sehnervenstammes II Teil die atrophischen Züstande des sehnerven. Klin. Monatsbl. f. Augenh., 55: 449–472, 1915.
12. Igersheimer, J.: Syphilis und Auge in Jadassohn, J.: Handbuch der Haut und Geschlechtskrankheiten. Berlin. Julius Springer, 17 (Pt. 2): 312, 350, 1928.
13. Fuchs, E.: The field of vision in tabetic atrophy of the optic nerve. Tr. Am. Ophth. Soc., 12: 718–727, 1911.
14. Paton, L.: Tabes and optic atrophy. Brit. J. Ophth., 6: 289–316, 1922.
15. Sloan, L. L.; Woods, A. C.: Perimetric studies in syphilitic optic neuropathies. Arch. Ophth., 20: 201–253, 1938.
16. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination. Grune and Stratton, New York. 1946. Pp. 56 and 81.

The Treatment of Decompensated Cardiovascular Syphilis with Penicillin [1]

Mortimer S. Falk, Joseph Edeiken, William T. Ford, and John H. Stokes [2]

In a recent communication from this clinic observations on 50 patients with penicillin-treated cardiovascular syphilis were presented (*1*). Although the number of patients treated was relatively small, statistically speaking, it was felt that there was strong evidence that penicillin is not contraindicated as initial therapy in syphilis involving the cardiovascular system. We have ventured one step further now and have administered penicillin to patients with cardiovascular syphilis in decompensation. This report records our observations on these patients during the following treatment.

In the prepenicillin era cardiac failure was considered by many to be a contraindication to any antisyphilitic treatment with the exception of iodides (*2*, *3*, *4*). Stokes and his associates differed from the majority in that they felt that patients with cardiovascular syphilis in decompensation did better when weak antispirochetal agents such as mercury were administered concurrently with measures to restore compensation (*5*). The consensus, however, is expressed in the following direct quotation from "The Modern Treatment of Syphilis" (*3*): "When decompensation is actually present on admission, the first essential is to treat the patient by the usual methods for dealing with congestive heart failure, before attempting more than the absolute minimum of antisyphilitic treatment. In the presence of failure, our practice is to limit specific treatment to usual (6 grams daily) doses of potassium iodide by mouth, and, if edema be troublesome and no contraindications exist, daily or tri-weekly injections of a usual dose of one of the mercurial diuretics, not only for its diuretic but also, and quite incidentally, for its antisyphilitic effect. Prolonged bed rest, slow convalescence and graduated exercise are all em-

---

[1] From the Institute for the Study of Venereal Disease, University of Pennsylvania, and U. S. Public Health Service cooperating, and the Penicillin-Syphilis Panel of the University Hospital. The Institute, The Robinette Foundation of the Department of Internal Medicine, the Departments of Neurology, Ophthalmology, Dermatology and Syphilology, and the Division of Venereal Disease Control, Philadelphia City Department of Public Health, and the Philadelphia General and Pennsylvania Hospitals are represented in the authorship.

The work described in this paper was done under a grant from the Research Grants Division of the National Institutes of Health in continuation of a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Pennsylvania.

[2] With the collaboration of Herman Beerman, Norman R. Ingraham, Jr., William O. LaMotte, and John W. Lentz, and the technical assistance of Verna Mayer Stein, Emily Stannard, Jane Barbara Taylor, and Mildred F. Wills.

ployed in the effort to build up some degree of cardiac reserve before the use of even moderately large doses of bismuth or of any dosages of an arsenical." This seemingly ultraconservative approach was formulated because several severe and even fatal reactions had been known to occur following the administration of arsenicals (*1, 6, 7, 8*). Herrmann and Jamison (*6*) outlined a method of treatment for patients in congestive heart failure which emphasized again the conservative approach. Their opinion was based on a long and extensive experience which included the observation of "some fatalities" following the direct use of even small doses of neoarsphenamine in decompensated cardiovascular syphilis. Herrmann and Wilson (*6*) observed electrocardiographic evidence of widespread myocardial disturbances directly following the introduction of arsenicals in the presence of congestive failure in patients with aortic syphilis.

Although there have been several reports on the treatment of cardiovascular syphilis with penicillin, a review of the literature revealed no references to the treatment of decompensated cardiovascular syphilis with penicillin. We have treated 12 patients who were in severe cardiac failure with penicillin. None of the patients was prepared with less potent spirocheticidal drugs. All were closely observed in the hospital under complete bed rest and low salt diet. Digitalis, ammonium chloride, and mercurial diuretics were started at the same time as the penicillin. The initial penicillin dosage ranged from 500 to 40,000 units every 2 hours and the total dosage from 4.8 to 9.6 million units of crystalline penicillin G. Examinations which included electrocardiograms and fluoroscopic studies were made before and at varying periods after penicillin treatment. The pertinent facts concerning each patient are outlined in tables 1 and 2.

Results

All of the 12 patients in cardiac decompensation tolerated penicillin without untoward reaction. The only evidence of therapeutic shock was slight febrile reactions in two patients: H.B. No. 7, starting 6 hours after initiation of penicillin therapy; and L.M. No. 12, starting 16 hours after the first injection. In no instance was it necessary to interrupt the treatment schedule. None of the patients showed signs of aggravation of the decompensated state. On the contrary, all seemed to be symptomatically improved within 48 to 72 hours after initiation of treatment. Electrocardiographic studies revealed T-wave abnormalities and other changes which could be attributed to digitalis but in no

instance was there evidence of intraventricular conduction defects. All of the patients were able to leave the hospital immediately on completion of penicillin therapy (usually in 10 to 12 days) in a markedly improved state. Maintenance dosages of digitalis were prescribed for all the patients and 7 were continued on mercurial diuretics. The posttreatment follow-up ranges from 2 to 21 months.

Two of our patients died 2 months and 3 months, respectively, following penicillin. The first patient, a 58-year-old white male, developed bilateral thrombophlebitis in the lower extremities and a pulmonary infarct. He died at home and autopsy was not obtained. The second patient, a 40-year-old Negro, had a very large heart (T.D. 18 cm.) and was badly decompensated on admission to the Institute. Although he was improved after treatment he subsequently relapsed and died at home 3 months after discharge from the hospital. The remaining 10 patients are still under observation in our out-patient clinic.

Discussion

We do not have sufficient evidence as yet to show that penicillin alters the course or prognosis of decompensated cardiovascular syphilis, but it is significant that the patients in this study were apparently able to tolerate large doses of a powerful spirocheticidal agent, even though they were in acute congestive failure when treatment was started.

It has been shown that penicillin is well tolerated by patients with late cardiovascular syphilis (*1, 9, 10*). In the paper previously alluded to (*1*) we reported our observations on 50 cases of late cardiovascular syphilis treated with penicillin. Physical examinations and electrocardiographic studies made before, during, and after treatment failed to disclose any deleterious effects upon the cardiovascular system as the result of this agent.

The apparent lack of toxicity of penicillin on the decompensated cardiovascular syphilitic is of great significance for it is this type of patient who received little or no antisyphilitic treatment before the penicillin era. The apparent innocuousness of the antibiotic is in striking contrast to the disastrous effects observed following arsphenamine. It is not unlikely that some of the fatalities which were attributed to the Jarish-Herxheimer reaction were due to the inherent toxicity of arsphenamine for an already damaged cardiovascular apparatus. Wilson, Wile, Shelly, Wishart, and Hermann (*8*) observed the development of an abnormal idioventricular rhythm following the administration of 0.2 gm. of arsphenamine

Table 1

	Case 1: V.H., [M], age 54, aortic regurgitation	Case 2: R.W., [M], age 67, aortic regurgitation	Case 3: P.L., [M], age 59, aortic regurgitation	Case 4: A.R., (?), age 47 aortic regurgitation hypertension	Case 5: W.R., [M], age 38 aortic regurgitation	Case 6: C.N., [M], age 43, asymptomatic neurosyphilis, aortic regurgitation	Case 7: H.B., [M], age 60, aortic regurgitation	Case 8: D.H., [M] age 60, aortic regurgitation, aneurysm ascending aorta	Case 9: V.R., [M], age 60, aortitis, hypertension	Case 10: B.M., [M], Age 49, aortic regurgitation, aneurysm innominate artery, hypertension tabes dorsalis	Case 11: P.O., [M] age 37, aortic regurgitation, Ca of larynx	Case 12: L.H. [M], age 66, aortic regurgitation
Duration of syphilis.	Unknown — at least 12 years.	Probably 45 years!	Unknown	Unknown.	23 years.	Unknown—at least 27 years.	Unknown.	20 years.	14 years.	30 years.	Unknown.	Unknown—probably 30 years.
Preparatilus treatment.	1937 10 Neo 10 Bi 1946 20 Mapharsen 1947 26 Bismuth.	Potassium iodide gtts. X daily to August 1918.	Hg. salicylicide. Potassium iodide. Bismuth. Mapharsen.	None.	Potassium Iodide. Bismuth 1940–41.	Arsphenamine) 12 injections, 1922.	Bismuth—40 injections.	Bismuth weekly for 4 years.	None.	4 arsphenamine 1910, 6 neoarsphenamine and Bi. 1913; Ac and Bi 1945–46.	None.	40 bismuth since 1945.
STS before treatment.	Kline 128 units.	Kline 256 units.	Kline 256 units.	Kline 128 units.	Kline 256 units.	Kline 256 units.	Kline less than 8 units.	Kline less than 8 units.	Doubtful.	Kolmer 44, Kahn 32 units.	Kahn 256 units.	Kolmer 44, Kahn 4 units.
STS after treatment.	Kline 128 units.	Kline 16 units.	———	Kline 128 units.	———	Kline 256 units.	———	Negative.	Negative	Kolmer 44, Kahn 128 units.	Kahn 16 units.	Kolmer 44, Kahn 8 units.
Amount and dosage of penicillin.	Crystalline "G": 10,000 o 6, (?) 40,000 o 116 Total 4.8 million u.	Crystalline "G". 5,000 x 8 10,000 x 4 40,000 x 18 Total 4.8 million u.	Crystalline "G": 10,000 x 8 40,000 x 118 Total 4.8 million u.	Crystalline "G" 10,000 x 8 40,000 x 118 Total 4.8 million u.	Crystalline "G": 10,000 x 8 40,000 x 110 Total 4.8 million u.	Crystalline "G": 500 x 12 1,000 x 12 8,000 x 12 40,000 x 110	Crystalline "G": 40,000 x 120 Total 4.8 million u.	Crystalline "G": 500 x 20 10,000 x 7 40,000 x 110 Total 4.8 million u.	Crystalline "G": 10,000 x 8 40,000 x 110 Total 4.8 million u.	Crystalline "G": 10,000 x 8 80,000 x 110 Total 8.8 million u.	Crystalline "G": 1,000 x 10 8,000 x 8 40,000 x 110 Total 4.8 million u.	Crystalline "G": 40,000 x 120 Total 4.8 million u.
Therapeutic shock.	None.	None.	None.	None.	None	None.	Slight temperature elevation.	None.	None.	None.	None.	Temperature 100° 18 hours after first injection.
Condition on discharge.	Improved.	Improved.	Improved.	Improved.	Improved.	Improved.	Improved.	Improved.	Improved.	Improved.	Improved.	Improved.
Present condition.	Improvement maintained 5 months post-penicillin.	Improvement maintained 4 months post-penicillin.	Dead 57 days postpenicillin.	Improvement maintained 10 months post penicillin.	Dead 3 months postpenicillin.	Improvement maintained 18 months post-treatment.	Improvement maintained 2 years post-treatment.	Improvement maintained 1 year post-treatment.	Improvement maintained 10 months post-treatment.	Improvement maintained 24 months post-treatment.	Improvement maintained 5 months post-treatment.	Improvement maintained 2 months post-treatment.

Table 2.—*Status of cardiovascular system prior to penicillin and at time of most recent examination*

	Case 1. A. H. (M), age 50, aortic regurgitation	Case 2. R. M. (M), age 57, aortic regurgitation	Case 3. P. J. (M), age 51, aortic regurgitation	Case 4. H. H., (F), age 47, aortic regurgitation, hypertension	Case 5. H. S. (M), age 51, aortic regurgitation	Case 6. O. N., (M), age 15, asymptomatic neurosyphilis, aortic regurgitation	Case 7. H. H., (M), age 59, aortic regurgitation	Case 8. H. H., (M), age 69, aortic regurgitation, aneurysm ascending aorta	Case 9. V. S., (M), age 50, syphilis, hypertension	Case 10. R. S. (M), age 49, aortic regurgitation, aneurysm innominate artery, hypertension and tabes dorsalis	Case 11. E. H., (M), age 67, aortic regurgitation, Ca of larynx	Case 12. L. H. (M), age 56, aortic regurgitation
BEFORE PENICILLIN												
Signs and symptoms	Angina since 1937, severe dyspnea and occasional orthopnea; marked pretibial edema, BP 171/90.	Progressive dyspnea for 2 years, orthopnea, marked ankle edema; liver enlargement 5 cm below costal margin; right pleural effusion, BP 160/30.	Severe angina and cardiac decompensation 2 years; right pleural effusion, moderate pretibial edema; BP 160/90.	Progressive dyspnea 2 years, ankle edema 6 months. Admitted to hospital in acute cardiac decompensation; rales both bases, liver moderately enlarged; marked pretibial edema; BP 160/70.	Angina pectoris 1 year; progressive dyspnea, orthopnea nocturnal dyspnea; heart enlarged, rales both bases; moderate ankle edema, BP 160/90.	Progressive dyspnea and orthopnea 6 months; right pleural effusion, liver moderately enlarged; moderate ankle edema, BP 150/60.	Angina, progressive ankle edema and dyspnea 6 years, nocturnal dyspnea, orthopnea, died relapsed 3 weeks before admission; BP 160/70.	Dyspnea 4 years, progressive orthopnea, nocturnal dyspnea, rales both bases, moderate liver enlargement; marked ankle edema; BP 120/80.	Progressive dyspnea; rales both bases, marked ankle edema; relieved by diuretin and mersalyl, marked hypertension; marked pretibial edema; BP 190/110.	Ankle edema, severe dyspnea, severe upper substernal pain, especially nocturnal, BP 195/120.	Ankle edema severe dyspnea, rales in both bases, liver enlargement, BP 160/50	Ankle edema, orthopnea, rales in both bases, liver enlarged, BP 160/60
Roentgen findings	Marked cardiac enlargement to left, aorta diffusely dilated.	Marked enlargement especially to left, aorta markedly and spirally dilated.	Marked cardiac enlargement; aorta dense and dilated	Marked enlargement; aorta moderately dilated.	Enlarged downwards to left, aorta diffusely dilated.	Markedly enlarged to left aortic dilatation.	Marked enlargement, aorta dilated and dense.	Heart only slightly enlarged, aorta dilated, aneurysm of ascending aorta.	Heart markedly enlarged; aorta generally dilated and elongated.	Marked enlargement of heart; aorta markedly dilated and dense; aneurysm innominate artery.	Marked enlargement of heart, aorta dilated.	Marked enlargement of heart and diffuse dilation of the aorta.
Electrocardiogram	Slight depression ST-T segments in most leads.	Auricular fibrillation, changes of type seen in left ventricular hypertrophy.	Auricular fibrillation, aurora myocardium abnormally.	Changes of type seen in left ventricular hypertrophy.	Changes suggestive of left ventricular hypertrophy.	Severe myocardial damage.	Signs suggesting left ventricular hypertrophy; minor grade heart block.	Severe myocardial abnormality; probable damage to anterior septum left ventricle.	Changes suggesting left ventricular hypertrophy; digitalis effects.	Changes suggesting left ventricular hypertrophy.	Numerous extrasystoles; left ventricular hypertrophy.	Signs suggesting hypertensive hypertension
AFTER PENICILLIN												
Signs and symptoms	5 months: No congestive failure, no dyspnea, no angina, BP 160/60.	4 months Marked improvement, slight dyspnea, slight ankle edema.	2 months Free of decompensation; no angina, then developed thrombophlebitis and pulmonary infarction; died	10 months Marked improvement; evidence of congestive failure, BP 210/80.	Died at home 2 months post-penicillin treatment; cause unknown	18 months Marked improvement	12 months Much improved, no evidence of congestive failure; no angina.	13 months Marked improvement; some dyspnea on exertion; no ankle edema	10 months Marked improvement; operation in operating room; no further need second day of treatment. No recurrence 10 months.	2 years Marked improvement with relief of symptoms, BP 200/110.	5 months: No relief in bases. Slight dyspnea on exertion.	2 months: Marked improvement moderate dyspnea on exertion; no nocturnal dyspnea.
Roentgen findings	Heart slightly smaller; T.D. 16.9 cm. compared with 18.5 cm.	Heart slightly smaller.	No follow-up.	Heart smaller to normal, but evidence of left ventricular hypertrophy.	No follow-up.	Heart slightly smaller; aorta same.	No change.	Heart normal in size; aorta same.	No change.	No change	No change.	No change.
Electrocardiogram	Some changes for digitalis effects.	Unchanged.	No follow-up.	Digitalis effects otherwise same	No follow-up.	Same.	No change.	None.	No change.	No change.	No change.	No change.
Cardiac treatment with penicillin	Digitalis; mersalyl diuretic	Digitalis; ammonium chloride, mersalyl diuretic,	Digitalis; ammonium chloride, mersalyl diuretic.	Digitalis; mersalyl diuretic	Digitalis; ammonium chloride, mersalyl diuretic.	Digitalis; ammonium chloride; mersalyl diuretic.	Digitalis; mersalyl diuretic,	Digitalis; ammonium chloride; mersalyl diuretic.	Digitalis; mersalyl diuretic.	Digitalis.	Digitalis; salyrgan oxygen; aminophyllin.	Digitalis, salyrgan, ammonium chloride; diuretin.
Cardiac treatment after penicillin	Digitalis	None	None.	Digitalis, ammonium chloride.		Same.	None.	None.	None	None.	Digitalis.	Digitalis and salyrgan.

to a syphilitic patient who electrocardiographically showed right bundle branch block; death occurred a few days later. Two other patients with syphilitic aortitis, with practically normal electrocardiograms, developed diphasic QRS complexes suggesting incomplete bundle branch block, following intensive arsphenamine therapy. We have treated a total of 85 cases, including the 12 with decompensation and 3 with healed myocardial infarctions, with penicillin, and although transient T-wave changes were noted, conduction defects, except those due to digitalis, were absent.

If the Jarish-Herxheimer reaction is accepted as the cause of most untoward reactions in patients with cardiovascular syphilis treated with arsphenamine, how then can we reconcile the apparent lack of reaction in the same type of patient treated with penicillin. It cannot be argued that the difference in mode of action of the two drugs on the spirochete could of itself account for this seemingly wide difference in toxicity. One has merely to note the frequent occurrence of Herxheimer reactions in patients with early syphilis treated with penicillin, to ascertain that penicillin is far more effective in producing this type of reaction than arsphenamine. This is a fertile field for investigation but it is quite possible that the difference lies in the inherent toxicity of arsphenamine for the damaged cardiovascular system.

It is not possible at the present time to predict what the long-term results of penicillin treatment upon decompensated cardiovascular syphilis will be. We might re-echo Dr. Moore's recent statement: "It seems to me essential to employ penicillin in the treatment of cardiovascular syphilis at least on an investigation basis in order to outline clearly its risks and, more important, its benefits, if any."

Summary and Conclusions

1. Twelve cases of syphilitic cardiovascular disease with congestive failure were treated with penicillin concomitantly with the usual treatment for cardiac decompensation.

2. No untoward reactions, except for slight early febrile reactions in two patients, were observed during treatment. The total dosage varied from 4,800,000 to 9,600,000 units. Three patients were started on 500- to 1,000-unit doses; 7 patients on 5,000 to 10,000 units; 2 patients received large initial doses—40,000 units every two hours.

3. There were two deaths, neither of which we believe could be directly attributed to penicillin.

4. All patients were improved on leaving the hospital. We

cannot yet state how much of this improvement was due to penicillin; longer and more extensive experience is needed. However, it is our impression that patients with syphilitic cardiovascular disease and decompensation react better to the combined treatment than those who receive only treatment for congestive failure.

References

1. Edeiken, J.; Falk, M. S.; Steiger, H. P.: Observations on penicillin-treated cardiovascular syphilis. Am. J. Med. Sc. (In press.)
2. Woodruff, I. O.: Cardiovascular syphilis. Am. J. Med., 4: 248, Feb. 1948.
3. Moore, J. E.: The Modern Treatment of Syphilis. Charles C. Thomas, Springfield, 1947.
4. White, P. D.: Heart Disease. Third Edition, MacMillan Company, New York, 1944.
5. Stokes, J. H.: Arsphenamine Treatment of Syphilis. M. Clin. North America, 5: 422, Sept. 1921.
6. Herrmann, G. K.; Jamison, C.: The treatment of cardiovascular syphilis with special reference to aortic regurgitation with congestive heart failure. Am. J. Syph., Gonor. & Ven. Dis., 15: 1, 1931.
7. Bristiman, A. L.: Sudden death in syphilis. Am. J. Syph., Gonor. & Ven. Dis., 16: 470, 1932.
8. Wilson, F. N.; Wile, U. J.; Shelly; Wishart, S. W.; Hermann, G. K.: Changes in electrocardiogram following the arsphenamine treatment of cardiac and aortic syphilis. Proc. Soc. Exper. Biol. & Med., 23: 275, 1926.
9. Russek, H. I.; Cutler, J. C.; Fromen, S. A.; Zohman, B. L.: Treatment of cardiovascular syphilis with penicillin. Ann. Int. Med., 25: 947, Dec. 1946.
10. Tucker, H. A.; Farmer, T. W.: Penicillin in cardiovascular syphilis. Arch. Int. Med., 80: 322, 1947.

Treatment of Cardiovascular Syphilis with Penicillin[1]

Gerald Flaum and Evan W. Thomas

From April 1944 to February 1949, 55 patients with cardiovascular syphilis have been treated with penicillin at the Rapid Treatment Center at Bellevue Hospital. There have been 45 patients with aortic insufficiency and 10 patients with aortic aneurysm. Some 35 additional patients were treated in whom a diagnosis of syphilitic aortitis was made. These patients are not included in this study because of the well-known difficulty in definitely establishing this diagnosis.

[1] From the Departments of Medicine and Dermatology and Syphilology, New York University College of Medicine, and the Departments of Medicine and Dermatology and Syphilology, Third Medical Division (New York University), Bellevue Hospital, New York, N. Y., and the Rapid Treatment Center, Bellevue Hospital, New York, N. Y.

Aided by grants from the U. S. Public Health Service.

Aortic Insufficiency (45 patients)

Among the 45 patients with aortic insufficiency there were 10 with aneurysmal dilatation of the aorta and 4 with saccular aneurysms. In 5 a diagnosis of coronary ostial stenosis was made.

Twenty-five of the patients had neurosyphilis, which was usually the primary reason for admission. Of these, 7 had asymptomatic neurosyphilis, 4 meningovascular syphilis, 6 tabes dorsalis, 2 tabetic optic atrophy, 3 taboparesis, and 3 general paresis.

The age on admission was 34 to 39 in 4 instances; the remainder scattered to 75 years, with 21 patients falling in the 50- to 59-year group. There were 36 males and 9 females; 28 were white, 13 black, 3 yellow and 1 Puerto Rican.

In 28 instances the diagnosis of heart disease was made on admission; in 8 it had been made less than 1 year before, and in 9 patients 1½ to 5 years before admission.

Aneurysm (10 patients)

Four of the 10 patients with aneurysms had saccular aneurysms and six had diffuse aneurysmal dilatation of the aorta.

Eight of the 10 patients had neurosyphilis: 1 asymptomatic neurosyphilis, 2 meningovascular syphilis (1 with gumma of the forehead), 2 tabes dorsalis, 1 tabetic optic atrophy, and 1 taboparesis.

The patients ranged in age from 43 to 71. There were 9 males, 1 female; 7 were white, 2 black, and 1 yellow.

In 6 patients the diagnosis was made on admission; in 4 the aortic lesion was known 1 to 2 years previously.

Symptoms

Fifteen of the 45 patients with aortic insufficiency denied symptoms of diminished cardiac reserve; 21 had symptoms of diminished cardiac reserve for varying periods preceding admission; 9 were in congestive heart failure on or just prior to admission; 5 of these had had previous bouts of failure.

Four of the 10 patients with aneurysm offered symptoms referable to the lesion; 6 were symptom-free.

Previous Antisyphilitic Treatment

Of the 55 patients, 14 were considered to have had "adequate" antisyphilitic therapy previously. In 22, previous therapy was grossly inadequate (9 had received only bismuth) ; 19 patients had

received no previous antisyphilitic therapy. Of the 36 patients who had received some treatment previously, 8 had received it within 4 months prior to admission; in the remainder the interval was more than 1 year.

Treatment

No instances of therapeutic shock in cardiovascular syphilis had been observed in this clinic with the older methods of treatment. It was thought wise, however, to start treatment in previously untreated patients with an agent less actively spirocheticidal than penicillin, in order to avoid the risk of a Herxheimer reaction. To this end, it had been decided early in this study to give 3 injections of bismuth subsalicylate in oil 5 to 7 days apart before starting penicillin. This plan was not adhered to, however, in all instances. Seven of the 19 patients who had had no previous antisyphilitic therapy received no preliminary bismuth, 1 received 1 injection, and 4 received 2. Of the 36 patients who had had some previous treatment, only 4 received 1 to 3 injections of bismuth.

In all patients penicillin was administered in full dosage from the start of treatment.

Thirty-seven patients received aqueous penicillin (2.0 to 6.0 million units), 6 received penicillin in oil and wax (4.2 to 9.0 million units), and 12 received procaine penicillin in oil (3.6 to 9.0 million units).

Results

No adverse reactions were encountered in these patients during penicillin therapy. Five patients with aortic insufficiency had one or more bouts of substernal or precordial pain during treatment. These episodes were never alarming and all had had previous similar symptoms. Two patients had 1 and 2 bouts of nocturnal paroxysmal dyspnoea during treatment; one of these was in congestive heart failure at the time of treatment, and both had had similar attacks for 6 to 12 months before admission. In no case was penicillin administration interrupted. No reactions of any kind were seen in the 10 patients with aneurysm.

Eleven of the 45 patients with aortic insufficiency were not seen after treatment. Seven are known to be dead. Of these 7, 2 died of unknown cause and 1 following gallbladder surgery. One patient died at another hospital less than 1 month after treatment of what was diagnosed as coronary occlusion; he had had several bouts of acute left ventricular failure in the 2 months prior to admission. Two patients died in congestive heart failure 1 and 2

months after treatment; both were in congestive heart failure at the time of treatment. The prognosis in these three patients was considered grave at the time of treatment. The seventh patient died of cerebral embolus after the onset of auricular fibrillation 15 months after treatment. The only necropsy was performed in the last case.

Of the remaining 27 patients, 5 have been followed for less than 6 months, 10 for 6 to 12 months, 4 for 13 to 23 months, and 8 for 24 to 43 months. Of these 27 patients, 13 were asymptomatic on admission and have remained so; 2 are definitely worse 31 and 7 months later; 2 are unchanged, and 10 claim to be improved. This improvement is completely subjective but is difficult to explain, particularly in one instance. This patient had had three bouts of congestive failure and was in failure on admission. Digitalis had been taken before treatment and has been continued since. He has been followed for 21 months and at present denies all symptoms of diminished cardiac reserve despite his work as a janitor, which requires him to walk three flights of steps daily and five flights once a week while carrying a bucket of water and a mop.

There is no follow-up on 4 of the 10 patients with aortic aneurysm. Two have died; 1 of rupture of the aneurysm 24 months after treatment, and 1 of pulmonary infection secondary to bronchial obstruction 9 months after penicillin. Two of the remaining 4 are asymptomatic, 1 is worse, and 1 patient who has four saccular aneurysms and who complained of dyspnoea on admission, claims to be improved.

The outcome of 3 of the 9 patients who were in congestive heart failure on, or just prior to, admission is unknown. Four are dead (1, 2, 7, and 15 months after treatment). One is well compensated 6 months after treatment, and 1 appears to be improved (see above).

The few instances of adverse reactions that have been reported in patients with cardiovascular syphilis treated with penicillin require no comment here. They include the cases of Moore (*1*), Dolkart and Schwemlein (*2*), Callaway (*3*), Scott (*4*), and their coauthors. Porter (*5*) described rupture of a large aneurysm of the thoracic aorta 2 days after the institution of penicillin therapy. In view of the many thousands of patients with all types of syphilis who have been treated with penicillin and the unknown number of patients with syphilis who have received penicillin for some other reason (as in Scott's case) we believe it significant that there are only these few reports of adverse reactions. Furthermore, the relationship between penicillin and the untoward reaction even in the reported cases is not a clear-cut one.

The total number of patients with cardiovascular syphilis treated with penicillin that has been reported to date (*6, 7, 8, 9*) is small and our own series does not augment it greatly. Nevertheless, we are in accord with the views of Tucker and Farmer (*8*), of Webster (*9*) and his group, and Moore (*10*) that the danger of therapeutic shock following the institution of penicillin therapy has been overemphasized.

The number of patients in this series who have reported subjective improvement is striking. We do not believe that this implies an improvement in their cardiovascular status, but rather that it reflects the sense of well-being seen so frequently in patients following the eradication of a chronic, low-grade, syphilitic infection.

Summary and Conclusions

1. Fifty-five patients with cardiovascular syphilis were treated with various amounts of penicillin given in full dosage from the start of treatment.

2. No instance of therapeutic shock was encountered.

3. Symptoms such as precordial pain and nocturnal paroxysmal dyspnoea occurred during treatment only in patients who had had similar symptoms prior to admission.

References

1. Moore, J. E.: Penicillin in Syphilis. Charles C. Thomas, Springfield, 1946.
2. Dolkart, R. E.; Schwemlein, G. X.: The treatment of cardiovascular syphilis with penicillin. J.A.M.A., 129: 515, 1945.
3. Callaway, J. L.; Noojin, R. O.; Flower, A. H.; Khun, B. H.; Riley, K. A.: Use of penicillin in the treatment of syphilis of the central nervous system. Am. J. Syph., Gonor. & Ven. Dis., 30: 110, 1946.
4. Scott, V.; Maxwell, R. W.; Skinner, J. S.: The Jarisch-Herxheimer phenomenon in late syphilis. J.A.M.A., 139: 217, 1949.
5. Porter, R. R.: Penicillin in cardiovascular syphilis. Virginia M. Monthly, 75: 357, 1948.
6. Russek, H. I.; Cutler, J. C.; Fromer, S. A.; Zohman, B. L.: Treatment of cardiovascular syphilis with penicillin. Ann. Int. Med., 25: 957, 1946.
7. Hill, W. R.: Problems arising in the treatment of syphilis with penicillin. New England J. Med., 235: 919, 1946.
8. Tucker, H. A.; Farmer, T. W.: Penicillin in cardiovascular syphilis. Arch. Int. Med., 80: 322, 1947.
9. Conferences on therapy: Treatment of cardiovascular syphilis. New York State J. Med., 49: 306, 1949.
10. Moore, J. E.: Cardiovascular syphilis. Am. J. Syph., Gonor., & Ven. Dis., 33: 1, 1949.

Aureomycin and Chloromycetin in the Therapy of Granuloma Inguinale[1]

Robert B. Greenblatt, Robert B. Dienst, Virgene Wammock, Calvin Chen, and Robert M. West

The University of Georgia group working on granuloma inguinale have attempted to evaluate the therapeutic effectiveness of the various antibiotics as they became available for trial. Penicillin proved of no value. Streptomycin has been used with excellent results. Aureomycin was found to be orally effective, and the response to this drug has been remarkable. Chloromycetin holds forth the promise of being the antibiotic of choice in the therapy of granuloma inguinale.

Streptomycin

One hundred and forty-two patients have been treated with streptomycin. The ideal dosage was found to be 20 gm. administered intramuscularly in doses of 1 gm. every 6 hours for 5 days. Seventeen relapses occurred but many of these responded to a second course of therapy. Five patients, however, failed to respond to two or more courses of streptomycin and were considered resistant to this drug.

Aureomycin

When aureomycin first became available to us for trial, intramuscular injections of 20 mg. were administered from one to six times per day for total dosages ranging from 420 mg. to 1,500 mg. Donovan bodies persisted in the lesions and no evidence of healing was observed. Oral aureomycin was then tried. Wright et al. however were able to obtain cures in two cases with aureomycin intramuscularly in doses of 2,020 mg. and 560 mg., respectively.

The dosage schedule for oral aureomycin was arbitrarily chosen, as 250 mg. every 6 hours for 5 days (5 gm.). Partial to complete healing seemed to take place within a few days. Donovan bodies however could be demonstrated many days after completion of therapy in biopsy sections of the scarred and presumably healing tissues. Relapses soon occurred with this dosage schedule and therapy was resumed and continued for periods ranging from 10 to 40 days. The five streptomycin-resistant patients yielded successfully to this therapeutic regime (table 1).

---

[1] From the University of Georgia School of Medicine.

Aided by grants from the State of Georgia Department of Public Health and the U. S. Public Health Service.

Table 1.—*Aureomycin therapy in streptomycin-resistant granuloma inguinale*

Case No.	Aureomycin (intramuscular)	Total dosage	Aureomycin (oral)	Total dosage	Results	Follow-up
		mg.		*gm.*		
1	(*a*) 20 mg./day/7 days	140			No healing	
	(*b*) 20 mg. t.i.d./8 days	480			No healing	
	(*c*) 20 mg. q.4 h./7⅓ days	880			No healing	
			(*d*) 250 mg. q.i.d./5 days	5.0	Healing incomplete	
			(*e*) 250 mg. 4–6/day/27 days	37.0	Healed after 18 days	Healed (7 mos.).
2	(*a*) 20 mg. t.i.d./7 days	420			No healing	
			(*b*) 250 mg. q.i.d./5 days	5.0	Healed-relapse	
			(*c*) 250 mg. 4–6/day/20 days	25.5	Healed after 11 days	Healed (7 mos.).
3	(*a*) 20 mg. q.4 h./8½ days	1,020			No healing	
			(*b*) 250 mg. q.i.d./14¼ days	14.25	Healing—slight relapse	
			(*c*) 500 mg. q.i.d./8 days	16.0	Healed after 2 days	Healed (7 mos.).
4 [1]			(*a*) 250 mg. q.i.d./5 days	5.0	Healed-relapse	
			(*b*) 250 mg. q.i.d./30 days	30.0	Healed [1]	Healed (7 mos.).
5			(*a*) 1 gm. q.i.d./5 days	20.0	20 percent healed	
			(*b*) 500 mg. q.i.d./10 days	20.0	80 percent healed	
			(*c*) 500 mg. q.i.d./5 days	10.0	90 percent healed	
			(*d*) 500 mg. q.i.d./10 days	20.0	Healed	Healed (4 mos.).

[1] Biopsies, however, revealed presence of Donovan bodies deep in tissue until fifteenth day.

Various dosage schedules were tried in an effort to standardize treatment. It appeared that about 20 gm. of the drug were necessary for cure. One gram every 6 hours for 5 days (20 gm.) was tried out but with this dosage the patients complained of nausea and vomiting. The schedule now in use is 500 mg. every 6 hours for 10 days (20 gm.). Whenever response to this dosage schedule was poor, therapy was continued until healing was more or less complete. In such instances the range of dosage was 30 to 70 gm. The therapeutic results have been excellent and the nausea minimal (table 2).

Table 2.—*Oral aureomycin in granuloma inguinale* [1]

Case No.	Aureomycin	Dosage	Results at completion of therapy	Follow-up
		gm.		
6	(20 mg. t.i.d./7 days intramuscularly)	0.42	No healing.	
	(a) 100 mg. q.i.d./7 days	2.8	Healing incomplete.	
	(b) 100 mg. q4h/13½ days	8.0	Healed.	Healed (7 mos.)
7	250 mg. q.i.d./32 days	32.0	Healed.	Healed (7 mos.)
8	250 mg 4-6/day/32 days	40.0	Healed in 21 days.	Healed (7 mos.)
9	1 gm. q.i.d./5 days	20.0	Healed 75 percent.	Healed (6 mos.)
10	1 gm. q.i.d./5 days	20.0	Healed 75 percent.	Relapse—3 mos.
	500 mg. q.i.d./10 days	20.0	Healed.	Healed (3 mos.)
11	1 gm. q.i.d./5 days	20.0	Healed 20 percent.	Healing incomplete 1½ mos.
	500 mg. q.i.d./15 days	30.0	Healed.	Healed (3 mos.)
12	500 mg. q.i.d./10 days	20.0	Healed 80 percent.	Healed (4 mos.)
13	500 mg. q.i.d./10 days	20.0	Healed.	Healed (3 mos.)
14	500 mg. q.i.d./10 days	20.0	Healed 70 percent.	
	500 mg. q.i.d./10 days	20.0	Healed.	Healed (3 mos.)
15	500 mg. q.i.d./10 days	20.0	Healed 80 percent.	
	500 mg. q.i.d./20 days	40.0	Healed.	Healed (3 mos.)
16	500 mg. q.i.d./10 days	20.0	Healed 90 percent.	Healed (4 mos.)

[1] 8 more patients in this series were successfully treated with dosages varying from 20 to 50 gm. A new series of 20 patients was started to whom 500 mg. q.i.d. for 12.5 days was given for a total of 25 gm. At the end of 1 month's observation all but one was healed.

Untoward Reactions

Intramuscular injections of aureomycin proved somewhat painful. Oral aureomycin in 250 mg. doses four times per day was well tolerated. In larger dosage nausea was a prominent feature.

Vomiting occurred in those cases where 1 gm. every 6 hours was employed.

Results

Sixteen patients with granuloma inguinale were successfully treated with oral aureomycin. Donovan bodies were demonstrated in each case before start of therapy. When the *"500 mg. every six hours for ten days"* dosage schedule was used, Donovan bodies disappeared from the lesions in 3 to 11 days. Healing usually proceeded to completion in 3 or 4 weeks in patients with extensive lesions. Complete healing was observed in 4 to 5 days in patients with small lesions. Some of these cases have been under observation for more than 4 months since healing occurred, and only one relapse has been observed after complete healing. This was in a patient who vomited much of her drug. She responded to a second course of 20 gm. of aureomycin in 10 days.

Chloromycetin

This drug only became available to us for trial in the past few months. Although in vitro studies were not as promising as that obtained with streptomycin and aureomycin, it was nevertheless deemed worthy of clinical trial. Five patients were selected for therapy (table 3). The dosage schedule in the first three cases

Table 3.—*Chloromycetin in therapy of granuloma inguinale* [1]

Case No.	Dosage	Total dose	Results at completion of therapy	Follow-up
		gm.		
1	0.5 gm. q.i.d./10 days	20	Healed.	
2	0.5 gm. q.i.d./10 days	20	90 percent healed.	Healed (4 mos.).
3	0.5 gm. q.i.d./10 days	20	Genital lesions healed but extragenital lesions did not completely heal.	Genital lesions healed 4 mos.
	0.5 gm. q.i.d./15 days	30	Good response to second course.	Extragen. lesions healed 2½ mos.
4	1 gm. q.i.d./5 days	20	90 percent healed.	Healed (4 mos.).
5	1 gm. q.i.d./5 days	20	Response slow.	
	0.5 gm. q.i.d./10 days	20	Healed after second course.	Healed (3 mos.).

[1] 9 more patients have been treated since this report was submitted. The dosages required for healing ranged from 20 to 50 gm.

was 500 mg. every 6 hours for 10 days. The lesions healed rapidly under this mode of treatment. In the last two cases 1 gm. every 6 hours for 5 days was employed. The results were equally as good. No nausea, vomiting, or other untoward reactions were observed. With this intensive dosage Donovan bodies disappeared

by the third day. The ideal dosage appears to range from 20 to 50 gm. depending on the response of the patient or the extensiveness of the lesion. Now that this drug has been synthesized, it may prove not only the most effective but also the most economic.

Conclusions

1. Oral aureomycin has proved a most effective antibiotic in the therapy of 16 patients with granuloma inguinale.

2. The ideal dosage appears to be 500 mg. every 6 hours for 10 days for a total of 20 gm., although 30 to 70 gm. may be required to cure extensive or recalcitrant lesions.

Mild nausea to severe vomiting has been experienced in some cases, especially when 4 gm. per day of oral aureomycin was administered.

4. Chloromycetin may prove to be just as effective as aureomycin in the therapy of granuloma inguinale. Five cases were successfully treated. The advantage of chloromycetin appears to be that nausea and vomiting do not occur in dosages used.

5. The dosage employed with chloromycetin was 2 to 4 gm. per day orally for a total of 20 gm., but as much as 40 to 50 gm. may be needed for cure in some cases.

6. More time must elapse before a final evaluation may be made of the effectiveness of aureomycin and chloromycetin.

Aureomycin: Its Oral Administration and Effect on *Treponema Pallidum* in Man[1]

Robert R. Kierland, Wallace E. Herrell, and Paul A. O'Leary

Aureomycin is an antibiotic recently developed by Duggar and his coworkers at Lederle Laboratories. It is active against a number of organisms and has shown promise in the treatment of a variety of infections. Our interest in the effects of aureomycin on syphilis was prompted by the work of Heilman (*1*) in our laboratory, wherein he has shown that aureomycin, weight for weight, is two to three times as effective as penicillin in experimental spirochetal infections, namely, relapsing fever (*Borrelia novyi*) and Weil's disease (*Leptospira icterohaemorrhagiae*).

We have treated six patients with syphilitic disease with aureomycin administered orally. Two patients had primary lesions (*2*). The first was a white man 38 years of age, who came to the clinic for examination because of a painless scrotal ulcer of 2

[1] From the Mayo Clinic, Rochester, Minn.

months' duration. In the past week an eruption of the lower lip, left axilla, palms, and soles had developed associated with malaise, sore throat, and headache. Examination revealed a large superficial ulceration measuring 4 cm. in diameter on the anterior surface of the scrotum, with the base and periphery of the ulcer being indurated. In addition, superficial erosions were present on the mucous membrane of the lower lip, there was a faint maculopapular eruption on the trunk, and an erythematous papular eruption was present on the palms and soles. The examination otherwise was noncontributory. Darkfield examination of material from the scrotal ulcer revealed the presence of *Treponema pallidum*.

The patient was hospitalized the same day and started on aureomycin (duomycin) at 8 p.m.; a dose of 400 mg. was given orally every 4 hours. The dose of aureomycin was increased to 500 mg. every 4 hours on the fourth hospital day. The patient received 750 mg. every 4 hours from the sixth through the seventh hospital days, and from then on he received 500 gm. every 4 hours throughout the rest of his hospitalization. The aureomycin given totaled 44.2 gm.

A febrile Herxheimer reaction was noted 24 hours after treatment with aureomycin was started. The results of the darkfield examination were negative 60 hours after aureomycin treatment was begun and remained negative. Twelve hours earlier there were but one or two sluggish *Treponema pallidum* organisms per microscopic field. The roseola was still present but the ulcer had begun to heal. In 96 hours the roseola had faded and the mucous patches had healed while the scrotal ulcer was rapidly healing. At the time of dismissal, 16 days after admission, all lesions had healed; however, there was residual induration at the site of the chancre.

Prior to the treatment, serologic reactions for syphilis were strongly positive and the titer was 256 Kahn units. Forty days after the onset of treatment the titer was 32 Kahn units. At 72, 103, and 135 days after treatment was started, the serologic tests for syphilis were negative.

Blood levels of aureomycin were checked at frequent intervals during therapy and varied between 2 and 4 micrograms per cubic centimeter of blood while the patient was receiving 400- and 500-mg. doses of aureomycin, but when the aureomycin was given in doses of 750 mg. every 4 hours the blood level was 8 micrograms per cubic centimeter.

The second patient, a white man aged 24, came to the Clinic for an examination because of a penile lesion of 1 week's duration. The ulcer measured 1 cm. in diameter and was located on the

anterior surface of the penile shaft. There was peripheral induration of the lesion. There was no roseola or other objective evidence of syphilis. The results of darkfield examination for *Treponema pallidum* were positive, and on serologic examination for syphilis, negative Kline, Kahn, and Kolmer reactions but a positive Hinton reaction were obtained.

Aureomycin (duomycin) was administered orally in the dose of 750 mg. every 4 hours for 15 days for a total dose of 67.5 gm. Twelve hours after beginning treatment the results of darkfield examination for *Treponema pallidum* were positive, but at 16 hours and thereafter they were negative. Four days after the beginning of treatment the primary lesion was 50 percent smaller. At the end of the treatment period the primary lesion was completely healed.

Blood levels for aureomycin varied between 2 and 4 micrograms per cubic centimeter. The only objective evidences of untoward reactions were nausea, anorexia, and, on one occasion, vomiting. At the end of the treatment there were mild perlèche and a smooth reddened tongue indicating beginning vitamin B deficiency.

Pretreatment serologic tests for syphilis were entirely negative; however, 8 days after the onset of treatment the serologic reactions had become positive and the quantitative Kahn units measured 8. Fourteen days after treatment was started there had been a reduction in the titer to 3 units and from the twenty-third through the one hundred and twenty-eighth day the serologic reactions were negative.

Two patients had late ulceronodular syphilodermata, the first of 10 years' duration and the second of 6 years' duration. Aureomycin was given to the first patient in a dosage of 250 mg. every 6 hours for 3 days, 500 mg. every 6 hours for 3 days, followed by 1 gm. every 6 hours to a total dosage of 56.5 gm. Also present was associated cardiovascular syphilis manifested by aortitis with regurgitation. The ulceronodular lesions healed rapidly during treatment.

The second patient, with similar ulceronodular syphilodermata, had no other objective evidence of syphilis, and his lesions, too, healed rapidly during the treatment period in which he received 60.0 gm. of aureomycin.

Two patients had central nervous system syphilis. One was unable to tolerate the aureomycin and it was discontinued; he was then given penicillin without untoward reaction.

The second patient tolerated aureomycin well and received a total dose of 90 gm. of the antibiotic. At this early date the results of this treatment are very encouraging.

Untoward reactions.—The untoward reactions noted to date have

been those referable to the gastrointestinal system and manifested by nausea, anorexia, and occasional vomiting. In only one patient of the six, however, did this reaction interfere with treatment. Stool specimens are rendered sterile by means of this drug and for this reason avitaminosis of mild degree may develop. It is suggested then that vitamin supplements be given during the therapeutic period.

In conclusion, aureomycin appears to have definite antitreponemal activity when administered by the oral route. It is much too early to tell what the progress of these patients will be and we have treated too few patients to determine any failure rate or incidence of either serologic or mucocutaneous relapse. Therapeutic comparisons between penicillin and aureomycin remain for the future.

References

1. Heilman, F. R.: Aureomycin in the treatment of experimental relapsing fever and *leptospirosis icterohaemorrhagica* (Weil's Disease). Proc. Staff Meet., Mayo Clin., 23: 569–573, Dec. 8, 1948.
2. O'Leary, Paul A.; Kierland, R. R.; Herrell, Wallace E.: The oral administration of aureomycin (duomycin) and its effect on *Treponema pallidum* in man. Proc. Staff Meet., Mayo Clin., 23: 574–578, Dec. 8, 1948.

Studies on the Effect of Aureomycin on *Treponema Pallidum*[1]

Richter H. Wiggall, Harold E. C. Zheutlin, E. Randolph Trice, DuMont F. Elmendorf, Jr., and R. C. V. Robinson

Many reports have appeared on the efficacy of aureomycin in various bacterial, viral and spirochetal infections. O'Leary, Kierland, and Herrell (*1*) reported two patients with early syphilis, and Irgang and Alexander (*2*) nine others, treated with aureomycin with favorable results. Organisms disappeared from open lesions in approximately 2 to 5 days, lesions healed, and positive serologic tests reverted to or toward negative.

Unpublished experiments of Nelson (*3*) indicate that in vitro, aureomycin has only one-thousandth the treponemal immobilizing effect of penicillin (0.1 gamma of penicillin G per milliliter was equivalent to 100.0 gamma of aureomycin). Nelson's work was followed by observations of the activity of the drug in rabbit and human syphilis, which are reported in the present communication.

[1] From the Johns Hopkins University and the U. S. Public Health Service Venereal Disease Research and Post-Graduate Training Center. Aided by a grant-in-aid from the Research Grants and Fellowships Division, National Institutes of Health, U. S. Public Health Service.

Aureomycin[2] in Experimental Syphilis in the Rabbit

Therapeutic Experiment

The technic employed was that described by Turner, Cumberland and Li (*4*) in evaluating the treponemicidal effect of penicillins G, F, K and X by the rate of disappearance of treponemes from cutaneous syphilomas in rabbits. Briefly, this procedure involved the intracutaneous inoculation of 0.1 cc. of an emulsion rich in *Treponema pallida* (Nichols strain) in 10 to 12 sites on rabbits'[3] shaven backs. Syphilomas ordinarily appeared at these sites in 10 to 14 days and were allowed to develop to a diameter of 10 to 15 mm. Darkfield preparations from expressed serum contained 1 to 6 treponemes per oil-immersion field. Prior to treatment and at 24-hour intervals counts were made on two typical syphilomas on each rabbit in the following manner: The lesion was grasped at its base with a hemostat to secure it and minimize bleeding. The top of the lesion was then sliced off with a thin, sharp razor blade, care being taken to cut through the substance of the syphiloma. This was done at two levels. A small amount of serum exuded from or was squeezed from the lesion, taken up on a cover slip and placed on a slide. The cover slip was pressed firmly on the slide to insure a thin preparation of uniform depth. One hundred fields in each of four specimens (two from each lesion) were examined and the highest number of treponemes counted was taken as the result of that particular observation. After the pretreatment count, freshly prepared aureomycin hydrochloride dissolved in isotonic saline, was injected intramuscularly.

The drug was administered every 4 hours in three equal doses. Total dosages used were 50, 100, and 200 mg./kg. Five rabbits were used in each series.

Baseline determinations were made to see if there was daily variation from the initial count in the untreated rabbit. Darkfield examination and counts were performed as described above. For a period of five days the number of treponemes in a fully developed syphiloma remained relatively unchanged and a composite curve of average treponeme counts from five rabbits showed a constant level (fig. 1).

After the injection of a total dose of 50 mg./kg. of aureomycin into rabbits, no appreciable decrease in the number of treponemes was observed within the first 24 hours. However, after 48 hours there was a decrease of from 50 to 90 percent in the treponeme counts. Within 72 hours the decrease was much more uniformly

[2] The aureomycin used in these studies was furnished by the Lederle Laboratories Division of American Cyanamid Co.

[3] The rabbits employed in these experiments were all adults of an average approximate weight of 2.5 kg.

marked, some of the lesions becoming darkfield negative and the majority of the remainder having only a few treponemes. Only an occasional lesion was darkfield positive in 96 hours.

Larger total doses of aureomycin (100 and 200 mg./kg.) did not alter the rate of disappearance. This is particularly evident from examination of composite curves for the three doses (fig. 1).

Ninety-eight percent of the organisms seen in pretreatment counts were actively motile. Aureomycin caused no increase in the number of nonmotile forms.

There was a concurrent decrease in the size of the lesions after treatment. Within 48 hours there was a slight decrease and this progressed so that by 5 days they were about one-fifth of the original size and at the end of 10 days the majority were completely healed. This is well shown in the following photographs (fig. 2). One rabbit was untreated; the other was given 100 mg./kg. of aureomycin divided in three doses. The initial lesions in both animals were approximately the same size.

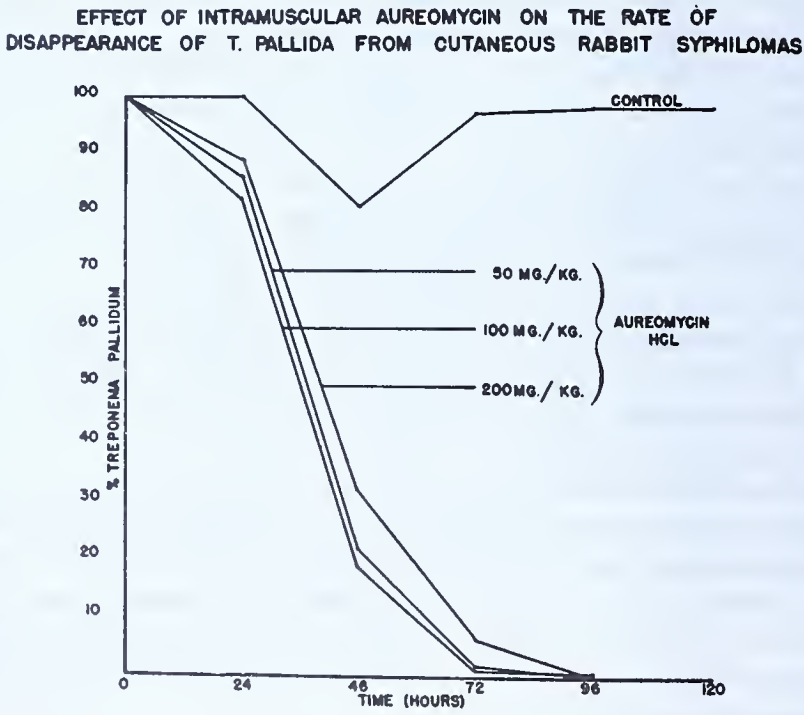


FIGURE 1.—Composite curves of treponeme counts expressed in percentage. Each curve represents the average of five rabbits.

Photographs taken on the fifth and tenth days demonstrate that the lesions in the control animal have increased in size and have ulcerated, while in the treated animal healing has occurred so that only an area of depigmentation remains.

These animals were discarded at about 10 days after treatment and are, unfortunately, not available for test of complete cure by lymph node transfer.

FIGURE 2.—The effect of aureomycin on the rate of healing in cutaneous syphilomas in rabbits. The upper pictures are of the control.

To face pg. 140

FIGURE 3.—The effect of aureomycin on the rate of healing in secondary syphilis and granuloma inguinale. The lower photograph was taken five days later.

To face pg. 141

Prophylactic (Early Abortive Treatment) Experiment

A second method of evaluating the effect of aureomycin was a protection test. Thirty rabbits, half of which were controls, were inoculated intratesticularly with 0.2 cc. of an emulsion rich in *T. pallida.* Within 5 minutes after inoculation, five animals were treated with a single injection of 12.5 mg./kg. of aureomycin; five with 25 mg./kg.; and five with 50 mg./kg. These doses were then repeated twice daily for 8 to 10 days. Table 1 gives details as to the incubation period of orchitis in the controls, and the length of observation for the aureomycin-treated groups. None of the rabbits receiving aureomycin developed orchitis or other evidence of syphilis.

Table 1.—*Early (abortive) treatment with aureomycin in rabbit syphilis*

Number of rabbits	Number surviving	Dosage (intramuscular) mg./kg.	Total dosage mg./kg.	Orchitis [1]	Average time of appearance of orchitis (days)	Observation time of treated rabbits (days)
5	5	No treatment (control)	0	+	24.5	
5	3	12.5 b.i.d. for 10 days	250	0		40
5	4	No treatment (control)	0	+	11.5	
5	4	25 b.i.d. for 10 days	500	0		42
5	5	No treatment (control)	0	+	18.4	
5	3	50 b.i.d. for 8½ days	850	0		64

[1] Lymph node transfers not yet done.

Lymph node transfers, to rule out asymptomatic infection will be done at 6 months after treatment. Serologic tests were not performed.

Aureomycin in Early Infectious Syphilis in Man

The effect of aureomycin on the lesions of early syphilis in man was first noted by us during an investigation of this drug in the treatment of granuloma inguinale. One patient (fig. 3) had both granuloma inguinale and secondary syphilis. Penicillin therapy was withheld for 72 hours to observe the effect of aureomycin. Within this time the condylomata lata were darkfield negative and had begun to involute.

On the basis of this observation, 15 patients were selected from cases hospitalized at the Baltimore rapid treatment center. Each presented one or more lesions of primary or secondary syphilis which were positive on darkfield examination. The lesions in each instance were large, moist, and readily accessible for repeated darkfield examinations.

Five of the patients were female. All were Negroes except case 14. Eight had primary lesions and seven secondary syphilis with condylomata lata.

Aureomycin hydrochloride in the form of 250-mg. capsules was given by mouth every 6 hours. The individual doses were either 0.5 gm. or 1.0 gm. No attempt was made to adjust dosage to the patient's weight.

Serial darkfield examinations were performed by two experienced physicians. Two or three preparations were examined carefully each day from each patient and at least 50 fields explored on each slide. Lesions which had become dry and epithelialized during the course of aureomycin treatment were abraded sufficiently to obtain serum for darkfield examination.

The results are tabulated in table 2. The first nine patients received either 2 or 4 gm. of aureomycin per day for only 2 days. At 24 hours after the start of treatment all lesions remained darkfield positive with no decrease in the number of treponemes. At 48 hours, 5 of the 9 patients were darkfield positive but in every instance only 1 to 2 *T. pallida* were found in each 50 fields.

Six patients were given 4 gm. of aureomycin daily for 6 days. During this period darkfield examinations were done daily (table 2). The lesions of all six patients became darkfield negative at 72 hours and remained negative during the total period of observation. The lesions of two patients (cases 10 and 12) healed completely in 6 days. The amount of healing in cases 11, 13, 14, and 15 was not significant by the sixth day, but the lesions were in general cleaner although not diminished in size or depth.

All 15 patients received 4.8 million units of penicillin at the end of the study period.

Toxicity of Aureomycin

No general statements can be made regarding toxicity in rabbits. In every large colony there are outbreaks of diarrhea, and unexplained deaths. It was our impression with this relatively small group that anorexia, diarrhea, and death rates were higher than one would expect. Three of the rabbits became paralyzed in the hind quarters. One of 21 control animals died, whereas 6 of 31 treated animals died.

Reactions to aureomycin in patients were minimal and consisted mainly of diarrhea, and nausea without vomiting. It was not necessary to discontinue administration of the drug to any patient. Diarrhea or relative increase in the number of stools was almost universal.

Discussion

Aureomycin is effective in experimental rabbit syphilis, both in the treatment of established early infections and in abortive

Table 2.—*Effect of oral aureomycin on* T. pallida *in lesions of early syphilis in man*

Case No.	History No.	Stage of disease	Duration of lesions	STS	Weight	Daily dose of aureomycin	Result of darkfield examination (hours after onset of aureomycin)							Appearance of lesions after 144 hours of aureomycin
							0	24	48	72	96	120	144	
			(*days*)	(*Eagle units*)	(*kg.*)	(*gm.*)								
1	125371	Primary	21	192	83	2.0	+	+	+					
2	126007	do	4	24	84	2	+	+	0					
3	125628	Secondary	14	48	45	2	+	+	+					
4	126156	do	21	256	50	2	+	+	0					
5	126189	do	14	48	44	2	+	+	+					
6	126218	do	14	48	65	4	+	+	+					
7	126229	do	21	48	60	4	+	+	0					
8	126276	Primary	5	0	68	4	+	+	+					
9	126540	do	7	0	70	4	+	+	0					
10	126547	Secondary	14	192	52	4	+	+	+	0	0	0	0	Completely healed.
11	126765	Primary	14	1	60	4	+	+	+	0	0		0	No change in size, shape or depth of ulcer.
12	126766	do	28	64	53	4	+	+	0	0				Completely healed.
13	126770	do	14	24	60	4	+	+	0	0				Ulcer smaller in size, less induration.
14	126773	do	14	48	60	4	+	+	+	0	0		0	Moist, eroded lesions persist.
15	126788	Secondary	42	256	60	4	+	+	0	0				Mucocutaneous plague dry and 10 percent smaller.

(prophylactic) treatment. In both early abortive and later treatment, the minimal effective dose has not yet been determined. Treponemes disappeared as rapidly from open lesions after a total dose of 40 mg./kg. as after four times this amount; and animals were as readily protected after 250 mg./kg. as by 850 mg./kg.

Since lymph node transfers were not made in the animals with established infections, and are not yet available in the group given early abortive treatment, it is not determined whether cure of established infections was accomplished, nor whether delayed or asymptomatic infections may yet appear in the group given early abortive treatment.

In animals or man the effect of aureomycin, in the dosages and by the routes employed, is slow relative to that of penicillin as measured by the disappearance time of organisms from open lesions and by the rate of the healing. Though definite comparisons of the minimal effective dose cannot be made at the present time, since that for aureomycin is not yet known, the in vitro data suggest that, in gravimetric terms, aureomycin may be less efficient than penicillin.

Dosage comparisons between animals and man may be difficult to assess. We have administered the drug to rabbits by the intramuscular route, since in this animal oral administration is difficult, and gastric physiology and perhaps absorption are different from those in man. The oral route has been used in man because of the intense local pain produced by intramuscular injections, and because of the satisfactory results of oral administration in other infections.

Lacking more definite information as to minimum effective dose of aureomycin in syphilitic infection in animals and man, as to the comparative effectiveness of aureomycin and penicillin, and as to final proof of cure or protection in animals, we have felt it undesirable to depend on aureomycin alone in the treatment of infected human beings, to all of whom a subsequent course of penicillin has been given. Moreover, considering the frailty of human nature, we still believe it to be undesirable to rely on any oral medication for the cure of syphilis in man, unless and until it can be shown that a single pill or capsule, swallowed under observation, is curative. For the present, therefore, the use of aureomycin in the treatment of syphilis should, in our opinion, be confined to further experimental studies.

Finally, if aureomycin is used for the treatment of any other venereal disease, since it appears to be effective in all, the possibility of suppression of simultaneously acquired but not yet evident syphilis must, as in the penicillin treatment of gonorrhea, be kept in mind.

Summary

1. Aureomycin, given intramuscularly to rabbits in total doses of 50, 100, and 200 mg./kg., produced a decrease of 50 to 90 percent in the number of treponemes in cutaneous syphilomas in 48 hours. Complete healing of the lesions occurred in about 10 days.

2. Aureomycin in doses of 12.5, 25, and 50 mg./kg. given twice daily for 8- and 10-day periods prevented the development of syphilitic orchitis following the intratesticular inoculation of an emulsion of *T. pallida.*

3. Orally administered aureomycin in daily dosages of 2 or 4 gm. resulted in the disappearance of *T. pallidum* from the lesions of early syphilis in 4 of 9 patients in 48 hours; in 6 of 6 in 72 hours; and appeared to produce local healing at the end of 144 hours in 2 of 6 patients.

References

1. O'Leary, P. A.; Kierland, R. R.; Herrell, W. E.: The oral administration of aureomycin and its effect on *Treponema pallidum* in man. Proc. Staff. Meet. Mayo Clin., 23: 574, 1948.
2. Irgang, S.; Alexander, E. R.: Treatment of early syphilis with aureomycin. Harlem Hosp. Bull., 1: 91, 1948.
3. Nelson, R. A.: Unpublished experiments, 1948.
4. Turner, T. B.; Cumberland, M. C.; Li, Huan-Ying: Comparative effectiveness of penicillins G, F, K, and X in experimental syphilis as determined by a short in vivo method. Am. J. Syph., Gonor. & Ven. Dis., 31: 476, 1947.

Report of Treatment with Fortified Penicillin of 248 Early Latent Syphilitic Mothers, and Follow-Up[1]

Belle Korman, Henry Eisenberg, Frederick Plotke, Hans Aron, and Jack Rodriquez

A study dealing with the outcome of 248 pregnancies of mothers with early latent syphilis was made to determine the adequacy of three different treatment schedules during pregnancy, based on penicillin reinforced with arsenoxide and bismuth, and the adequacy of re-treatment during pregnancy of previously treated

[1] From the Venereal Disease Control Program, Chicago Board of Health, in cooperation with the U. S. Public Health Service.

Under the direction of Herman N. Bundesen, Senior Surgeon (R) (Inactive), U. S. Public Health Service; President, Chicago Board of Health.

mothers with syphilis. All patients were hospitalized during treatment at the Chicago Intensive Treatment Center; the treated mothers and their infants were observed in the clinics of the Chicago Health Department; for a limited number of patients and infants follow-up data from other sources, when available, were utilized. Infants were examined at ages of 6 weeks, 3 months, 6 months and 1 year. Two hundred thirteen or 92.6 percent were followed for at least 3 months, 176 or 76.5 percent for 6 months, and 120 or 52.2 percent for 1 year or more.

Treatment schedule A (8-1.2-3) consisted of 1.2 million units of penicillin of various fractions administered intramuscularly in 60 injections of 20,000 units in aqueous solution every 3 hours for 7½ days, with concurrent administration of 8 doses of 40 mg. of arsenoxide and 3 doses of 200 mg. of bismuth subsalicylate. Schedule B (4-2.4-3) consisted of 2.4 million units of penicillin G in 60 injections of 40,000 units in aqueous solution every 3 hours, with 4 doses of arsenoxide and 3 of bismuth subsalicylate. Schedule C (4-4.8-3) consisted of the same quantities of arsenoxide and bismuth subsalicylate with 4.8 million units of penicillin G in 60 injections of 80,000 units every three hours.

The relative effectiveness of these 3 schedules in preventing prenatal syphilis in infants of 164 mothers with previously untreated early latent syphilis is compared in table 1. Treatment

Table 1.—*164 cases of early latent syphilis treated during pregnancy*

Schedule	Total patients	Nonsyphilitic live births		Disasters probably not due to syphilis			Disasters probably due to syphilis		Congenital syphilis
		Full term	Prematures	Abortions	Stillbirths	Neonatal deaths	Abortions	Stillbirths	
A (8-1.2-3)	41	36			1	2		1	1
B (4-2.4-3)	97	91	3		1	1	1		
C (4-4.8-3)	26	24			2				

was begun before the sixteenth week in 21 mothers, between the sixteenth and thirty-first in 103 mothers, and during the thirty-second week or later in 40 mothers. Only one case of congenital syphilis occurred in the infant of a mother treated with schedule A, given during the twenty-fifth week of pregnancy, the smallest amount of penicillin used. There were 154 infants who remained nonsyphilitic in spite of the fact that 53 of these mothers were seroresistant during observation after pregnancy, and 8 exhibited serologic relapse. Autopsies were performed in each case of neonatal death, none of which revealed evidence of syphilis.

Among the 5 stillbirths, there was adequate obstetric cause in 1, and autopsy revealing no evidence of syphilis in 1. One stillbirth and one late abortion were probably due to syphilis.

A group of 84 mothers was re-treated during pregnancy because of persistently positive serology or serologic relapse prior to re-treatment (table 2). These patients met the criteria of early latent syphilis at the time of re-treatment although during the pre-

Table 2.—*84 cases of early syphilis re-treated during pregnancy*

Schedule	Total patients	Nonsyphilitic live births		Disasters probably not due to syphilis			Congenital syphilis
		Full term	Prematures	Abortions	Stillbirths	Neonatal deaths	
A (8-1.2-3)	6	4		1			1
B (4-2.4-3)	50	45		3	2		
C (4-4.8-3)	28	23	3	1		1	

ceding two or three years they had received varying quantities of treatment for early infectious or early latent syphilis. In this group, one syphilitic infant was born, also after treatment of the mother with schedule A, given during the thirty-fourth week of pregnancy. Autopsy in the case of neonatal death showed no evidence of syphilis, and among the two stillbirths, there was adequate obstetric cause in one, and autopsy with no evidence of syphilis in one.

It may be concluded that, although we believe that not less than 3.6 to 5.4 million units, the minimum recommended by Moore, should be used, in our study, penicillin in at least 2.4 million units reinforced with arsenicals and bismuth subsalicylate was effective in preventing prenatal syphilis even though administered late in pregnancy to mothers who, in a high proportion, remained seroresistant after treatment.

The Effect of Caronamide on Penicillin Blood Levels[1]

A Comparative Study of 288 Males Given One-Day Treatment for Uncomplicated Gonorrheal Urethritis with Penicillin Alone, Caronamide Alone, and Penicillin Combined with Caronamide in Single and Multiple Oral Doses

Jack Rodriquez, Theodore J. Bauer, Frederick Plotke, W. W. Harris, and S. Weinstein

Introduction

Ever since penicillin was heralded as a potent therapeutic weapon many investigators have studied methods by which to prolong its therapeutic effectiveness either by delaying its absorption from an intramuscular depot or inhibiting its excretion through the renal system. This study deals with the latter mechanism. Beyer (*1*) and others (*2*) have shown that approximately 20 percent of renal clearance of penicillin is accomplished through glomerular filtration and 80 percent by way of renal tubular excretion.

It is further postulated (*1, 2, 3, 4*) that an enzyme transport mechanism is necessary and responsible for penicillin excretion through the renal tubules. Studies with caronamide[2] gave evidence that this drug was capable of blocking or inhibiting exclusively this enzyme transport mechanism for penicillin excretion while being itself uninfluenced by this enzyme transport mechanism and, furthermore, being limited in its own excretion to glomerular filtration. These and other studies reported (*5, 6, 7, 8*) show that caronamide has an enhancing effect on penicillin plasma levels.

The excretion of penicillin by the renal tubules can also be inhibited by the competitive mass action principle by other agents such as iodopyrine (*9*), diodrast (*9, 10, 11*), para-aminohippuric acid (*11, 12, 13*), benzoic acid and sodium benzoate (*14, 15, 16*), but necessity of administering large quantities of these drugs intravenously has limited their usefulness. Only the latter two can be administered orally and on the basis of studies conducted

---

[1] From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health, in cooperation with the U. S. Public Health Service. Under the direction of Herman N. Bundesen, Senior Surgeon (R) (Inactive), U. S. Public Health Service; President Board of Health.

NOTE: We wish to acknowledge our indebtedness to Sharp and Dohme, Inc., Philadelphia. Their grant-in-aid and supply of caronamide made this study possible.

[2] Caronamide is 4-carboxyphenylmethanesulfonanilide.

by Boger and Baker (*17*) it was concluded that "benzoic acid given in doses of 16 and 24 gm. per day . . . failed to increase penicillin plasma concentrations."

The aim of caronamide and many other devices is to achieve an enhancing effect on penicillin concentrations in body tissues to a point of therapeutic effectiveness in respect to the pathogenic organism in question. Lacking a chemical method of estimating quantitatively the amount of penicillin in tissue fluids we rely on "an inhibiting effect" of penicillin on certain test organisms as our standard of assayable units of penicillin in tissue fluids. At the present time it appears that 0.03 units per cubic centimeter has been the generally accepted "therapeutic level." But the fallacy in this can be readily seen when one considers that a split sample of blood reading 0.03 Oxford units per cubic centimeter when assayed by a highly sensitive serial dilution method may read 0.0 units per cubic centimeter when assayed by a less sensitive technic. The "therapeutic effective" blood level varies with the test organism used in the assay method, and may be extremely high in diseases produced by organisms highly resistant to penicillin, and then again in other diseases, such as gonorrheal urethritis,[3] the "therapeutic effective" level can be lower than detectable with present day assay methods. The curve of penicillin blood levels studied following 300,000 units intramuscular procaine penicillin in 2 percent aluminum monostearate, using the Rosenblatt and Loewe technic, will average approximately 24 hours (unpublished studies at the Chicago Intensive Treatment Center) as against approximately 96 hours when using the more sensitive cup assay method or the serial dilution assay method of Rammelkamp or modifications thereof. It is, therefore, important to recognize that the type of penicillin level curve resulting from a given study is as much the product of the kind of assay technic being used as it is of the antibiotic studied. Since the studies presented herein are assayed by the Rosenblatt and Loewe method, using the test organism *Streptococcus pyogenes* strain C-203, group A, it is to be expected that the peak concentration will appear lower and the duration of assayable penicillin in the blood serum less than with technics using more sensitive assay methods. However, this should not be construed to mean that the one assay method is superior to the other. The very sensitive assay methods may unwittingly lead one to assume a sense of false security in the judgment of the time-dose relationships.

---

[3] Unpublished studies at the Chicago Intensive Treatment Center show 100-percent satisfactory results in 13 male patients with gonorrheal urethritis given 150,000 units oral penicillin every 3 hours for 8 doses. Blood samples taken 1½ hours after each dose for 7 patients, and every 3 hours for 6 patients, failed to show assayable penicillin in 90.8 percent.

The effect of caronamide alone upon the estimation of penicillin serum levels was determined in 5 patients given 3 gm., and 11 patients given 6 gm. of caronamide in 2 doses of 3 gm. each 1 hour apart. Blood samples for penicillin assays were obtained in the 16 patients ½, 1, 2, 3, 4, 5, 6, 8, and 10 hours after the caronamide administration. No evidence of inhibition was observed on the test organism *S. pyogenes* strain C-203 used in the determination of penicillin serum levels in our laboratory (Rosenblatt and Loewe assay method) in any of the above samples.

There was no observable clinical or laboratory improvement in these same 16 patients in regard to the course of their acute gonorrheal urethritis. All had to be treated with penicillin after 3 to 5 days postcaronamide evaluation.

Average caronamide serum levels were obtained in 11 patients taken at intervals of 1, 2, 3, and 4 hours following a single oral dose of 6 gm. The average milligrams of caronamide per 100 cc. of serum were 8.3, 14.0, 16.8, and 14.5 at the end of the first, second, third, and fourth hours respectively. The highest reading at the end of the third hour was 27.9 mg./100 cc. and the lowest 4.2 mg./100 cc. Figure 1 shows the peak blood level of caronamide occurring at the end of the third hour and only a slight drop at

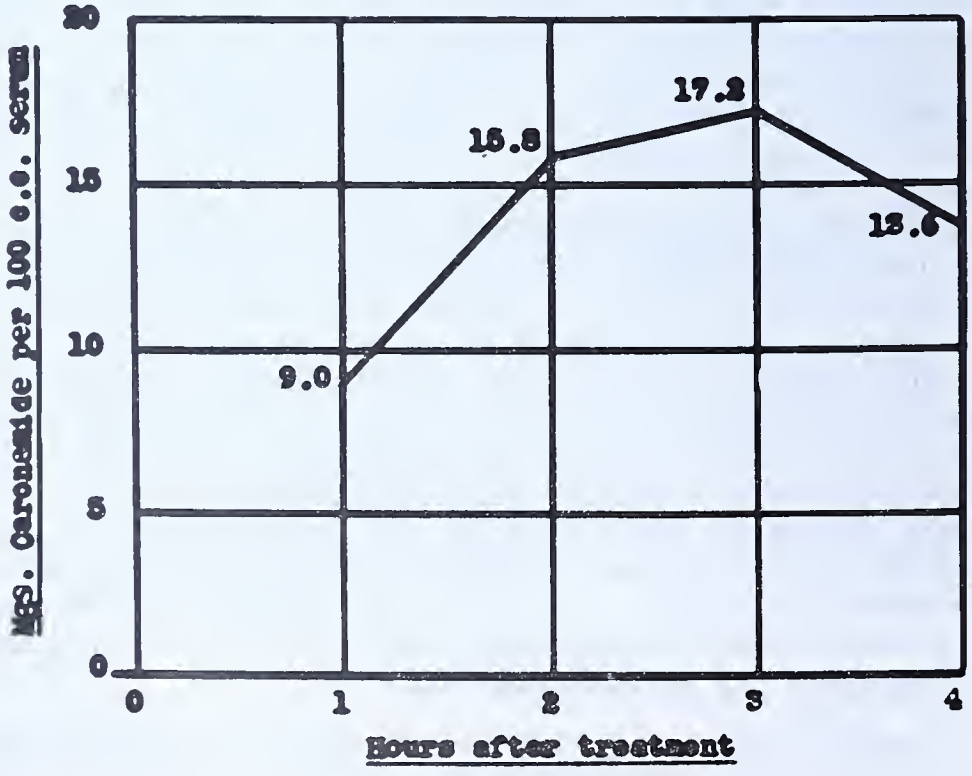


FIGURE 1.—Average caronamide blood levels of 11 patients given 6 gm. orally.

the end of the fourth. It is apparent that for most patients caronamide is readily absorbed through the gastrointestinal tract. It is reasonable under the conditions of this study to assume that caronamide is slowly excreted and conversely remains in the circulating blood for longer periods than 4 hours.

It is the purpose of this study to evaluate the inhibitory effect of caronamide on the renal eliminations of penicillin as determinable by the effect of caronamide on penicillin serum levels and the therapeutic effectiveness in uncomplicated gonorrheal urethritis in the male. Control studies are provided for each phase of the research. Part I of this report treats with those patients on the single-dose study, and part II with those patients on the multiple-dose study.

Part I

Single-Dose Schedules

Clinical Material

Table 1 shows the distribution of 214 male patients having acute uncomplicated gonorrheal urethritis by schedule variation, race, and age. Seven white males are included among the 214 patients. The youngest was 15 years and the oldest 51. The median for the whole group was 22.

Clinical and Laboratory Procedures

The diagnosis of uncomplicated gonorrheal urethritis in the male was established by positive smears and cultures. In addition, the following pretreatment routine was established: History, physical, Kahn, complete blood count, urinalysis, icterus index, and nonprotein nitrogen. At 10:00 a.m. of the first day following completion of the pretreatment routine, the patient was given oral penicillin, or oral penicillin plus caronamide with or without a previous priming dose of caronamide in accordance with a specified schedule. Blood samples for penicillin serum levels were drawn ½, 1, 2, 3, 4, 5, 6, 8, and 10 hours after the 10:00 a.m. dose. On the first, second and third posttreatment days smears and cultures were repeated. Evaluation of clinical response to treatment was made on the third and fourth posttreatment days and the patient discharged on the fifth posttreatment hospital day. All positive culture material was run through sugar fermentation for definitive diagnosis. On the first and third posttreatment days, leucocytes, hemoglobin, and urine tests were repeated; on the third, icterus index and nonprotein nitrogen. Patients were watched at all times for reactions to the caronamide. Patients with negative

Table 1.—*Patients grouped by treatment schedule, date of treatment, race, and age*

Schedule	Number of patients	Dates of treatment	Race		Age in years	
			White	Negro	Range	Median
Total	261	2-27-47 to 5-26-48	7	254	15-62	22
Single dose						
Total	214	2-27-47 to 2-17-48	7	207	15-51	22
A. 600,000 units penicillin:						
Without caronamide						
1. Control group	5	2-27-47 to 3- 7-47		5	18-30	23
With caronamide—						
2. 3 gm. with penicillin	5	2-28-47 to 3- 7-47		5	18-33	21
B. 1,200,000 units penicillin:						
Without caronamide—						
1. Control group	64	3-11-47 to 6-12-47	1	63	17-51	23
With caronamide—						
2. 3 gm. with penicillin	25	3-11-47 to 4-17-47	1	24	15-48	21
3. 6 gm. with penicillin	24	12-16-47 to 2-17-48		24	16-27	21
4. 3 gm. priming 1 hour 3 gm. with penicillin	26	4-22-47 to 6- 3-47	1	25	17-29	22
5. 3 gm. priming 2 hours 3 gm. with penicillin	40	6- 4-47 to 7- 2-47	1	39	17-38	23.5
6. 3 gm. priming 3 hours 3 gm. with penicillin	25	7-30-47 to 8-15-47	3	22	17-40	24
Multiple dose						
Total	47	3- 2-48 to 5-26-48		47	15-62	22
C. 500,000 units penicillin:						
Without caronamide—						
1. Control group	23	4-14-48 to 5-26-48		23	16-62	23
With caronamide—						
2. 10 gm. with penicillin	24	3- 2-48 to 4- 6-48		24	15-38	21

clinical and laboratory (smears and cultures) findings were considered satisfactory treatment results.

Treatment Schedules

From February 27, 1947, to February 17, 1948, a total of 214 patients was treated by the treatment schedules shown in table 1.

In schedule A 600,000, and in schedule B 1.2 million units of oral crystalline penicillin G were administered. A1 and B1 in each schedule constitute the control group where 600,000 and 1.2 million units of oral penicillin alone were administered. In schedule A2, B2, 3 gm., and in B3 6 gm. of caronamide were administered simultaneously with oral penicillin. In schedules B4, B5 and B6 the 10:00 a.m. doses were the same, namely, 1.2 million units of oral penicillin and caronamide, grams iii. An additional priming dose of caronamide, grams iii, was given at 9:00 a.m. (1-hour priming dose) in schedule B4, at 8:00 a.m. (2-hour priming dose) in schedule B5, and at 7:00 a.m. (3-hour priming dose) in schedule B6. The number of patients in each schedule, race and median age are shown in table 1.

Results of Treatment

A Schedules.—Five patients in schedule A1 were administered 600,000 units of oral penicillin alone and five patients in schedule A2 the same oral dose of penicillin concomitantly with 3 gm. of caronamide. When four out of five patients in A1 and A2 were observed to be clinical and laboratory failures, the A schedules were abandoned. No attempt to evaluate caronamide is being made on the basis of this small group.

B Schedules.—Schedule B1 constitutes a group of 64 patients who received 1.2 million units of penicillin in one single oral dose at 10:00 a.m. This constitutes the control group. In this schedule the average peak concentration level of penicillin in the serum was 0.532 Oxford units per cubic centimeter occurring at the end of the first hour (table 3). The median duration of assayable penicillin was 4.0 hours. Seventy-one and nine-tenths percent of the patients showed satisfactory outcome. The average percentage of patients showing penicillin serum levels in this and other B schedules is shown in table 2 and figure 2.

Table 2.—*1,200,000 units oral penicillin with and without oral caronamide—percentage of patients showing penicillin blood levels*

Schedule	Number	Hours after penicillin								
		1/2	1	2	3	4	5	6	8	10
Without caronamide:										
1. Control group	64	80.6	93.5	90.5	82.3	68.7	43.7	14.1	0	0
With caronamide:										
2. 3 gm. with penicillin	25	88.0	95.8	100.0	91.7	84.0	62.5	44.0	4.0	4.0
3. 6 gm. with penicillin	24	58.3	87.5	95.8	91.7	87.5	75.0	54.2	33.3	4.2
4. 3 gm. priming 1 hour 3 gm. with penicillin	26	73.1	92.3	96.1	96.1	84.6	76.9	50.0	23.1	0
5. 3 gm. priming 2 hours 3 gm. with penicillin	40	97.5	97.5	90.0	87.5	75.0	27.5	12.5	0	0
6. 3 gm. priming 3 hours 3 gm. with penicillin	25	92.0	96.0	96.0	92.0	80.0	68.0	16.0	0	0

In schedule B2, 1.2 million units of oral penicillin and 3 gm. of caronamide were administered in a single dose at 10:00 a.m. The average peak concentration level of penicillin was 0.694 occurring at the end of the second hour (table 3 and figure 3). The average duration of assayable penicillin was 5 hours. Eighty percent of the patients in this group showed satisfactory results.

In schedule B3, where 6 gm. of caronamide was given simultaneously with 1.2 million units of penicillin orally, the peak

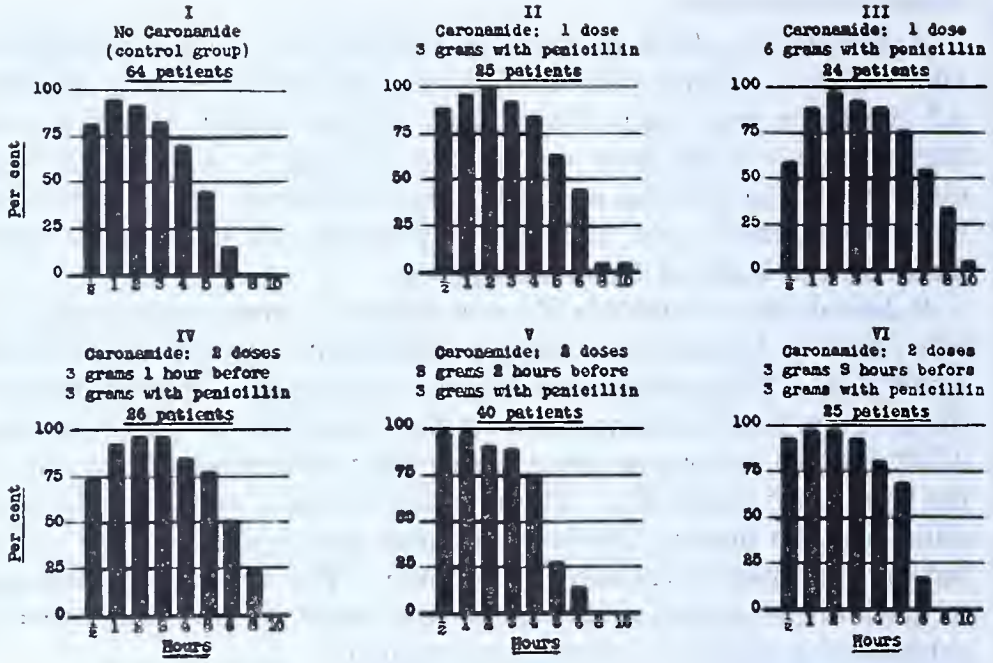


FIGURE 2.—1,200,000 units oral penicillin with and without oral caronamide. (Percentage of patients showing penicillin blood levels.)

concentration level of penicillin was 0.750 Oxford units per cubic centimeter occurring at the end of the second hour. The average duration of assayable penicillin was 6 hours. Eighty-seven and one-half percent of the patients in this group had a satisfactory outcome.

In schedule B4, where 1.2 million units of penicillin was administered with 3 gm. of caronamide at 10:00 a.m. and a 1-hour

Table 3.—*1,200,000 units oral penicillin with and without oral caronamide—average penicillin blood levels*

Schedule	Number	Units penicillin per c.c. serum at specified hours after penicillin									Detectable hours (median)	Success (percent)
		1/2	1	2	3	4	5	6	8	10		
Without caronamide:												
1. Control group	64	0.219	0.532	0.310	0.107	0.039	0.016	0.005	0.000	0.000	4.0	71.9
With caronamide:												
2. 3 gm. with penicillin	25	.233	.537	.694	.198	.098	.038	.013	.001	.001	5.0	80.0
3. 6 gm. with penicillin	24	.114	.448	.750	.449	.216	.097	.044	.017	.002	6.0	87.5
4. 3 gm. priming 1 hour 3 gm. with penicillin	26	.422	.730	.586	.381	.198	.112	.028	.006	.000	5.5	88.5
5. 3 gm. priming 2 hours 3 gm. with penicillin	40	.243	.497	.278	.140	.044	.014	.004	.000	.000	4.0	92.5
6. 3 gm. priming 3 hours 3 gm. with penicillin	25	.262	.327	.274	.133	.054	.024	.005	.000	.000	5.0	76.0

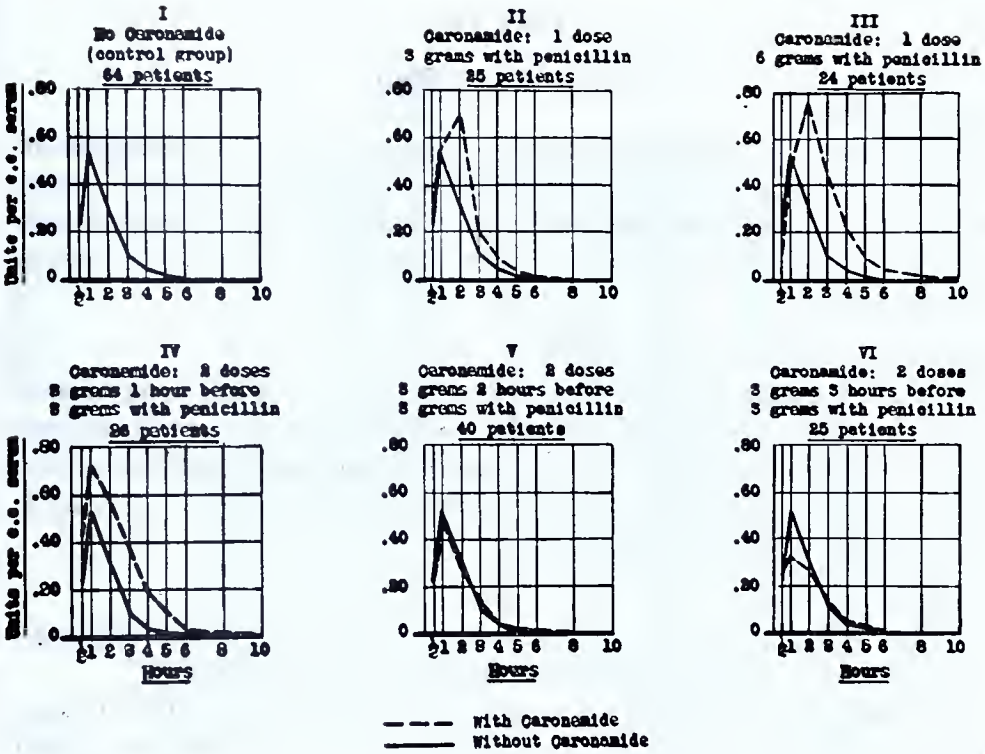


FIGURE 3.—1,200,000 units oral penicillin with and without oral caronamide. (Average penicillin blood levels.)

priming dose of caronamide of 3 gm. was given at 9:00 a.m., the average peak concentration level of penicillin was 0.730 Oxford units per cubic centimeter occurring at the end of the first hour and the average duration of assayable penicillin was 5.5 hours. A satisfactory outcome was observed in 88.5 percent of the patients in this group.

In schedule B5, where 1.2 million units of penicillin was administered with 3 gm. of caronamide at 10:00 a.m. and a 2-hour priming dose of caronamide of 3 gm. was given at 8:00 a.m., the average peak concentration level of penicillin was 0.497 Oxford units per cubic centimeter occurring at the end of the first hour and the average duration of assayable penicillin was 4 hours. Ninety-two and one-half percent of the patients in this group showed satisfactory results.

In schedule B6, where 1.2 million units of penicillin was administered with 3 gm. of caronamide at 10:00 a.m. and a 3-hour priming dose of caronamide of 3 gm. was given at 7:00 a.m., the average peak concentration level of penicillin was 0.327 Oxford units per cubic centimeter occurring at the end of the first hour and the average duration of assayable penicillin was 5 hours. Seventy-six percent of the patients in this group showed satisfactory results.

Part II

Multiple-Dose Study

Clinical Material

Table 1 shows the distribution of 47 male patients having acute uncomplicated gonorrheal urethritis by schedule variation, race, and age. All patients included were Negroes. The youngest was 15 years old and the oldest 62. The median for the whole group was 22 years.

Clinical and Laboratory Procedures

The clinical and laboratory procedures have been outlined in part I and remain unchanged for the patients in the multiple-dose study, with the exception of the blood samples for penicillin serum levels which were drawn 1 hour after each dose and ½, 1, 2, 3, and 4 hours after the final dose.

Treatment Schedules

From March 2, 1948, to May 26, 1948, a total of 47 patients was treated by the multiple-dose schedule shown in table 1.

In schedule C1 100,000 units of oral crystalline penicillin G was administered every 3 hours for five doses, i.e., at 10:00 a.m., 1:00 p.m., 4:00 p.m., 7:00 p.m., and 10:00 p.m., the total being 500,000 units of penicillin.

In schedule C2 100,000 units of crystalline penicillin G concomitantly with 2 grams of caronamide were administered orally at 10:00 a.m., 1:00 p.m., 4:00 p.m., 7:00 p.m., and 10:00 p.m., totaling 500,000 units of penicillin and 10 gm. of caronamide in five doses.

The number of patients in each schedule, race, and average age are shown in table 1.

Results of Treatment

C Schedules.—Schedule C1 constitutes a group of 23 patients serving as the control for the multiple-dose study. A study of table 4 and figure 5 shows the average penicillin-serum levels 1 hour after each dose, namely, 0.033 Oxford units per cubic centimeter after the first, 0.020 after the second, 0.053 after the third, 0.011 after the fourth, and 0.078 after the fifth dose of oral penicillin. The lowest average reading was 0.011 and the highest 0.078. The percentage of patients showing penicillin varied from a low of 26.1 percent 1 hour after the fourth dose to a high of 87.0 percent 1 hour following the third dose. Satisfactory results were observed in 73.9 percent in this control group.

In schedule C2 where 24 patients received 100,000 units of penicillin and 2 gm. of caronamide every 3 hours for 5 doses, the

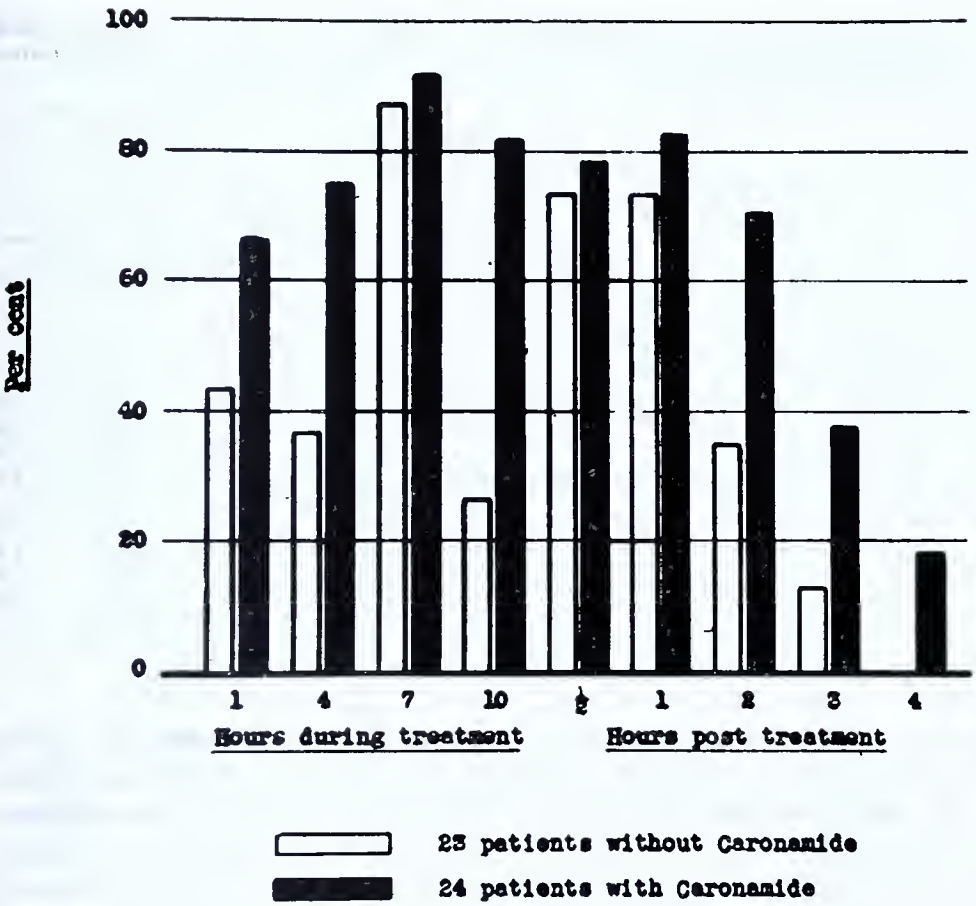


FIGURE 4.—500,000 units oral penicillin with and without 10 gm. oral caronamide: Five doses at 3-hour intervals—penicillin 100,000 units, caronamide 2 gm. (Percentage of patients showing penicillin blood levels.)

average penicillin serum levels were 0.065 units after the first, 0.051 after the second, 0.086 after the third, 0.060 after the fourth, and 0.081 after the fifth dose. The lowest average reading was 0.051 and the highest was 0.086. The percentage of patients showing penicillin varied from a low of 66.7 percent 1 hour after the first dose to a high of 91.7 percent 1 hour following the third dose. Ninety-five and four-fifths percent of the patients in this group were classified as satisfactory.

Reactions

The laboratory procedures performed for the evaluation of reactions are outlined in part I under "Clinical and Laboratory Procedures." One hundred and eighty-five patients were given from 3 to 10 gm. of caronamide. There were no clinical or skin manifestations observed in any of these patients which could be construed to indicate a reaction to caronamide. No laboratory evidence indicating visceral complications was observed in any of

Table 4.—*500,000 units oral penicillin with and without 10 grams oral caronamide—five doses at 3-hour intervals: penicillin 100,000 units, caronamide 2 grams*

Time at which specimens were drawn	Percentage of patients showing penicillin blood levels		Average penicillin blood levels		
			Units per c.c. serum		
	Penicillin alone (control)	Penicillin with caronamide	Penicillin alone (control)	Penicillin with caronamide	Fold increase
Number of patients	23	24	23	24	x
During treatment:					
1 hour after —					
First dose	43.5	66.7	0.033	0.065	2.0
Second dose	36.4	75.0	.020	.051	2.5
Third dose	87.0	91.7	.053	.086	1.6
Fourth dose	26.1	81.8	.011	.060	5.5
Posttreatment (after fifth dose):					
½ hour	73.9	78.3	.055	.068	1.2
1 hour	73.9	82.6	.078	.081	1.0
2 hours	34.8	70.8	.013	.037	2.8
3 hours	13.0	37.5	.008	.021	2.6
4 hours	0	18.2	.000	.005	.....

the 185 patients receiving from 3 to 10 gm. of caronamide. This was based on pre- and posttreatment icterus index in 177 patients, nonprotein nitrogen in 170 patients, leucocyte count, hemoglobin in 183 patients, and urinalysis for albumin and microscopic in the 185 patients. Caronamide crystals were not observed in any of the 185 posttreatment urine specimens. In 75[4] out of 185 patients pre- and posttreatment urines were tested for the presence of a reducing substance with negative results. Transient toxic reactions such as nausea, vomiting, rigors, fever, maculopapular and erythematous eruption as reported by others did not occur in this series.

Summary

1. Caronamide alone in the dosage described had no therapeutic effect on gonorrheal urethritis.

2. Caronamide alone in the dosage described had no demonstrable effect on the penicillin assay performed by the Rosenblatt and Loewe method utilizing *S. pyogenes* strain C-203, group A as the test organism.

3. Caronamide blood serum levels following a single dose of 6 gm. showed a peak concentration at the end of the third hour of 17.2 mg. per 100 cc. and only a moderate drop to 13.6 mg. at the end of the fourth hour.

[4] This includes 24 patients in C2 having had 10 gm. of caronamide.

4. In the single-dose schedules A1 and A2 it was quite obvious that 600,000 units of oral crystalline penicillin G alone or with 3 gm. of caronamide was ineffective in the treatment of acute gonorrheal urethritis in the male.

5. Figure 3 and table 3 demonstrate the effect of caronamide on the penicillin serum level as compared to schedule B1, the control group in the single-dose B schedules. Three grams of caronamide (B2) with 1.2 million units of penicillin effects a higher average peak serum level of penicillin concentration occurring at the end of the second hour and prolongs the median hours of assayable penicillin. This reaches the highest point in the next schedule, B3, when 6 gm. of caronamide is given with 1.2 million units of penicillin. In schedule B4, where 3 gm. of caronamide

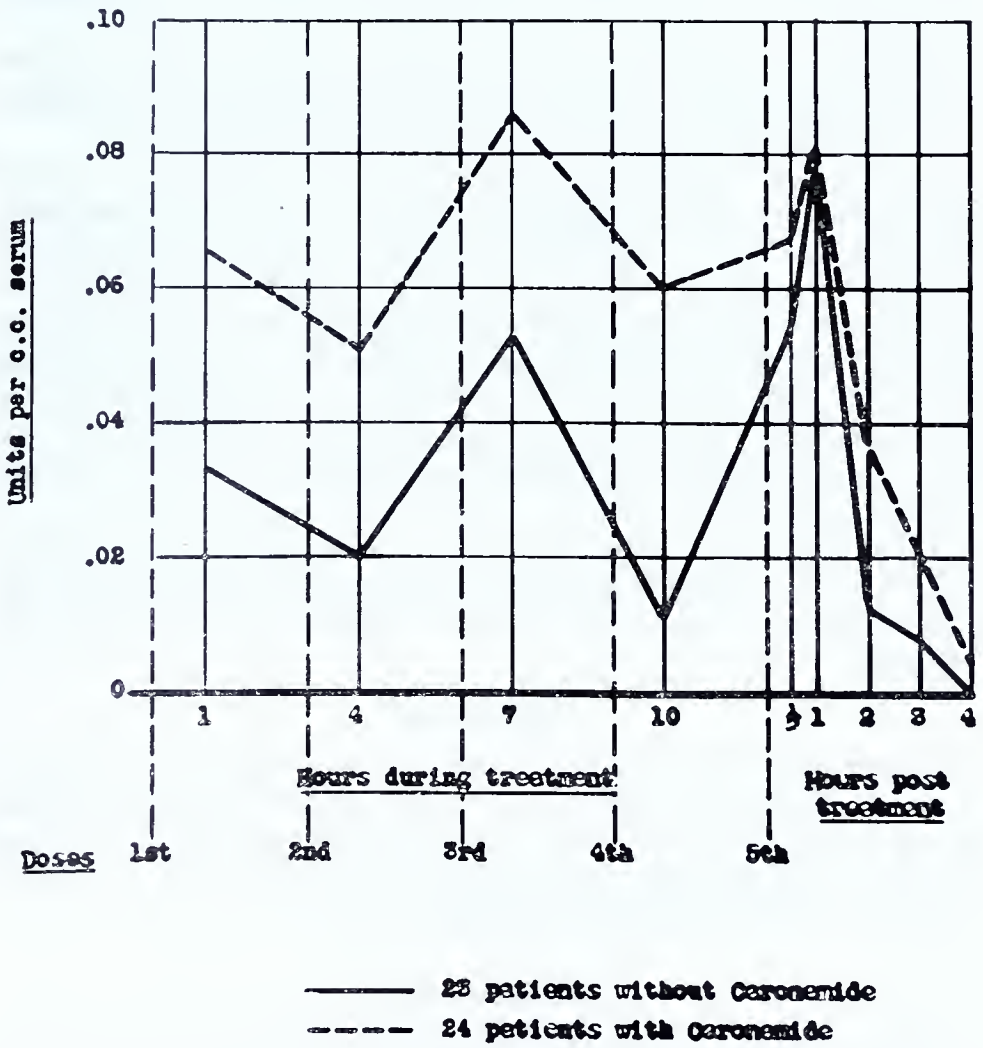


FIGURE 5.—500,000 units oral penicillin with and without 10 gm. oral caronamide: Five doses at 3-hour intervals—penicillin 100,000 units, caronamide 2 gm. (Average penicillin blood levels.)

is primed 1 hour, the average peak serum level of penicillin concentration falls back to the first hour but maintains its level almost on par with B3. In schedule B5, where 3 gm. of caronamide was primed 2 hours, the average penicillin level curve is almost superimposed on the control curve and in schedule B6 the curve falls below that of the control.

Generally the caronamide and penicillin schedules were moderately superior to the control in their therapeutic effectiveness, higher peak level of penicillin concentration in the blood, higher percentage of patients showing penicillin blood levels, and more prolonged median hours of assayable penicillin.

6. It is probable that in single oral dose administration, 3 gm. of caronamide or less cannot be uniformly relied upon to build a sufficiently high blood level to effect renal inhibition of penicillin excretion.

7. It is indicated that in single oral dose administration, 6 gm. of caronamide may be relied upon to build sufficiently high blood levels to effect renal inhibition of penicillin excretion.

8. In the multiple-dose study, an analysis of figures 4, 5, and table 4 shows a consistent superiority of the caronamide and penicillin schedules over the control. This is shown by the higher average penicillin concentration levels which varied from over 1 to 5.5 times as much as the control, the greater percentage of patients showing assayable penicillin and a significant superiority in the therapeutic effectiveness. It is noted that caronamide has a plateauing-like effect on the level of penicillin concentration in the blood as contrasted to the erratic and spiking curve produced by the control.

9. It is indicated that in multiple-dose schedules 2 gm. of caronamide every 3 hours is probably the minimal amount which is still effective in its ability to inhibit renal tubular excretions of penicillin.

Conclusion

On the basis of the increased therapeutic effectiveness in gonorrheal urethritis in the male, and the enhancing effect on penicillin serum level concentrations, it is concluded that caronamide has an inhibitory effect on the renal tubular mechanism for penicillin excretion. No reactions were noted.

References

1. Beyer, K. H.: New concept of competitive inhibition of the renal tubular excretions of penicillin. Science, 105: 94, Jan. 24, 1947.
2. Rake, G.; Richardson, A. P.: Pharmacology of penicillin. Ann. New York Acad. Sc., 48: 143, Sept. 27, 1946.

3. Rapoport, M.; Corneal, F. B.; Beyer, K. H.; Verwey, W. F.: A clinical evaluation in children of the toxicity and efficacy of caronamide (4-carboxyphenylmethanesulfonanilide) for the competitive inhibition of penicillin excretion. Am. J. M. Sc., 215: 514, May 1948.
4. Crosson, J. W.; Boger, W. P.; Shaw, C. C.; Miller, A. K.: Caronamide and penicillin. J. A. M. A., 134: 1528, Aug. 30, 1947.
5. Boger, W. P.; Baker, R. M.: A comparison of effect of caronamide and benzoic acid on penicillin plasma concentrations. Proc. Soc. Exper. Biol. & Med., 66: 1, Oct. 1947.
6. Boger, W. P.; Kay, C. F.; Eisman, S. H.; Yeoman, E. E.: Caronamide; compound that inhibits penicillin excretion by renal tubules applied to treatment of subacute bacterial endocarditis. Am. J. M. Sc., 214: 483, July 1947.
7. Seeler, A. O.; Wilcox, C.; Finland, M.: Enhancement of blood levels by caronamide during intramuscular administration of penicillin. J. Lab. & Clin. Med., 32: 807, 1947.
8. Strauss, E.; Richburg, P. L.; Saba, P. Z.; Alexander, J. E.: Enhancement of plasma penicillin concentrations by caronamide and sodium benzoate. J. Lab. & Clin. Med., 32: 818, 1947.
9. Rammelkamp, C. H.; Bradley, S. W.: Excretion of penicillin in man. Proc. Soc. Exper. Biol. & Med., 53: 30, May 1943.
10. Mokotoff, R.; Brams, W.; Katz, L. N.; Howell, K. M.: The treatment of bacterial endocarditis with penicillin. Am. J. M. Sc., 211: 395, 1946.
11. Avery, N. L., Jr.; Mayer, O. B.; Nelson, R. C.: Massive doses of penicillin in the treatment of subacute bacterial endocarditis. Ann. Int. Med., 24: 900, 1946.
12. Beyer, K. H.; Flippin, H.; Verwey, W. F.; Woodward, R.: The effect of para-aminohippuric acid on plasma concentration of penicillin in man. J.A.M.A., 126: 1007, 1944.
13. Loewe, L.; Rosenblatt, P.; Alture-Werber, E.: A refractory case of subacute bacterial endocarditis due to veillonella gazogenes clinically arrested by a combination of penicillin sodium paraaminohippurate and heparin. Am. Heart J., 32: 327, 1946.
14. Spaulding, E. H.; Bondi, A., Jr.; Early, E.: The effect of combining sodium benzoate with oral penicillins. Science, 105: 210, 1947.
15. Bronfenbrenner, J.; Favour, C. B.: Increasing and prolonging blood penicillin concentrations following intramuscular administration. Science, 101: 673, 1945.
16. Bohls, S. W.; Cook, E. B. M.; Potter, R. T.: Oral and parenteral use of aluminum penicillin mixtures in the treatment of gonorrhea. J. Ven. Dis. Inform., 27: 69, 1946.
17. Boger, W. P.; Baker, R. M.: A comparison of effects of caronamide and benzoic acid on penicillin plasma concentrations. Proc. Soc. Exper. Biol. & Med., 66: 1, October 1947.

Report on Penicillin-Treated Patients with Optic Atrophy

J. V. Klauder and B. A. Gross

This paper will appear in the "American Journal of Syphilis, Gonorrhea, and Venereal Diseases" during 1949.

Preliminary Observations on the Treatment of Early Syphilis, Utilizing Procaine Penicillin with Aluminum Monostearate[1]

Arthur G. Schoch

(These observations will be reported in detail at a later date.)

[1] Dallas Syphilis and Venereal Disease Schedule and the Southwestern Medical Foundation.

The Validity of Withholding Treatment in the Presence of Dattner-Thomas Formula in the Spinal Fluid[1]

S. F. Horne[2]

The concept of the "inactive" spinal fluid examination and the term "Dattner-Thomas formula" is now widely used by syphilologists. According to Dattner, Thomas, and others (*1, 2, 3, 4*) the spinal fluid which meets the criteria of inactivity is one which shows no abnormality except a positive test for syphilis in low titer (10 units or less) in a patient whose disease is more than 5 years old and who has received no treatment for at least 6 months. The above concept further assumes that a neurosyphilitic process is inactive in the presence of a normal cell count and total protein content accompanied by a positive serologic test in low titer, irrespective of the presence or absence of symptoms and/or signs (*1, 2, 3, 4*). Furthermore, it is assumed that little or no improvement in symptoms or signs and spinal fluid abnormalities can be expected from additional treatment.

Method of Study

During the past 4 years we have treated 11 patients who had spinal fluid abnormalities of the Dattner-Thomas type. These

[1] Presented by title at the symposium, *Recent Advances in the Investigation of Venereal Diseases*, held in Washington, D. C., on April 7–8, 1949, under the auspices of the Syphilis Study Section of the National Institutes of Health.

This paper represents work done under a contract between the Committee on Medical Research of the Office of Scientific Research and Development and the University of Michigan; and later supported by a grant-in-aid from the Research Grants Office, National Institutes of Health, United States Public Health Service. Part of the expense for this study was defrayed by the Babcock Urological Research Fund.

[2] Department of Dermatology and Syphilology, Medical School, University of Michigan.

patients were followed for 10 to 30 months subsequent to treatment. Four of the patients had paresis, six had tabes dorsalis, and one had taboparesis. All of the cases were acquired syphilis except one tabetic who had congenital syphilis. Seven of these (Nos. 1, 2, 3, 4, 6, 10, 11) had received at least minimal adequate chemotherapy before our initial examination, but no patient had received this therapy while he had early syphilis. One patient (No. 10) had received 1,400,000 units of penicillin, one (No. 4) had received a large amount of tryparsenamide and artificial fever therapy, two (Nos. 1 and 7) had received aldarsone, and one (No. 3) had had 10 treatments in a fever cabinet. Four patients (Nos. 1, 3, 4, 10) had received active antisyphilitic therapy within 6 months of our spinal fluid examination.

Five of our eleven patients were treated with penicillin alone, and six with penicillin and malaria. Two patients received 2,000,000 units (40,000 every 3 hours) of penicillin. The others were given 4,000,000 units of penicillin alone or the same amount of penicillin and a course of tertian malaria according to schedule previously described (*5*).

Results

The results of study of these patients have been presented in chart form in table 1. Because the prognosis of a patient with taboparesis is essentially that of his paresis, the one patient with that diagnosis is grouped with the patients with general paresis.

Subjective improvement was measured by statements from the patient that he had two or more of the following: Increased feeling of well-being, improved appetite, loss of insomnia, relief of lightning pains, less nervousness, improved ability to concentrate, a feeling of greater security and improvement in ataxia. Objective improvement was based, in general, on objective collaboration of the patient's opinion. It includes return to normal of reflex activity, improvement in dysarthria, retention and memory, improvement in ataxia, gain in weight and change in mental attitude. Information was gained from the patient's family and/or friends as well as from the patient.

We fully realize the immense difficulty in evaluating subjective and objective improvement and believe that the spinal fluid examination is a more reliable measure of improvement or lack of improvement. However, we do not believe that clinical findings can be disregarded. They must form some part of the evaluation of neurosyphilis.

Table 1.—*Summary of patients reported*

[The history regarding previous treatment is dated from the time of treatment by us. The patients who received penicillin and malaria received 4,000,000 units of penicillin and approximately 50 hours of fever over 103.5° rectally. The "time" is related to our treatment, "0" being pretreatment examination and the others representing examinations done at intervals (months) after treatment.]

Patient No.	Diagnosis	Previous treatment	Treatment	Time months	STS	Results			Spinal fluid examinations						
						Subjective	Objective	Spinal fluid	Cells	Total protein mg. per-cent	Globulin	Colloidal gold curve	Kahn	Presumptive Kahn	Kolmer
1	Paresis	172 Bi., 12 As[2], 67 aldarsone during past 5 years.	Penicillin and malaria.	0	0				4	41	+	0000000000	4	+	0
				9	±	[1] Imp.	Imp.		4	[2] ND	±	1223300000	0	0	ND
				18	0	Imp.	Imp.	Imp.	0	53	ND	0000000000	0	0	ND
2	Paresis	1 i.m.[3] and 1 i.v.[4] each week for 2 years, ending 7 years ago.	Penicillin (4,000,000)	0	0				4	41	4+	0000000000	4	+	0
				3	0	Imp.	Same		4	41	4+	0000000000	4	+	0
				12	ND	ND	ND	Imp.	0	ND	3+	0121000000	0	0	ND
3	Paresis	During the preceding year had 1 i.v. and i.m. each week and 10 treatments in fever cabinet.	Penicillin and malaria	0	1				4	27	0	0000000000	4	+	ND
				5	3	Imp.	Same		0	26	0	0000000000	4	+	ND
				10	±	Imp.	Imp.		0	26	0	0000000000	0	0	4----
				14	2	Normal	Normal		1	23	0	0000000000	0	±	0
				18	0	Normal	Normal		0	33	0	0000000000	0	0	0
				24	0	Normal	Normal		ND	ND	ND	ND	ND	ND	ND
				32	0	Normal	Normal	Imp.	1	27	+	0011000000	0	0	0
4	Paresis	Large amount of arsenic, bismuth and tryparsenamide and 24 treatments in fever cabinet.	Penicillin (2,000,000)	0	0				4	30	0	0000000000	4	+	ND
				3	0	Imp.	Imp.		2	34	±	0000000000	4	+	ND
				10	0	Imp.	Imp.		0	54	0	0000000000	4	+	0
				24	0	Clinically well			6	33	ND	0000000000	ND	ND	0
				39	0	Clinically well		Same	0	34	ND	0000000000	ND	ND	0
5	Tabo-paresis	15 i.v. injections 26 years ago.	Penicillin and malaria	0	40				0	33	2+	0011000000	4	+	0
				4	80	Imp.	Imp.		5	27	2+	1110000000	20	+	0
				12	32	ND	ND		ND	28	3+	0133210000	4	+	0
				18	32	ND	ND		ND	36	ND	0012210000	20	+	ND
				24	8	Same	Same	Worse	ND	ND	ND	ND	20	ND	ND

6	Tabes dorsalis.....	5 i.v. and 5 i.m. 6 years, 1 year alternating courses of As and Bi, 4 years ago.	Penicillin (2,000,000)	0	10	.....	.....	.....	2	35	0	0000000000	4	+	0
				24	4	Clinically well		Same	ND	ND	±	0121000000	4	+	0
7	Tabes dorsalis.....	Ki, 32 Bi., 22 aldarsone over 2 year period ending 1 year ago.	Penicillin (4,000,000)	0	80	.....	.....	.....	0	31	±	0022110000	4	+	ND
				1	80	Imp.	Imp.	.....	10	ND	+	0022100000	4	+	ND
				3	80	Imp.	Imp.	.....	0	ND	0	0011000000	4	+	ND
				6	20	Same	Same	.....	0	27	±	0011000000	4	+	0
				9	80	Same	Same	.....	4	25	+	0110000000	4	+	+±---
				12	160	Same	Same	.....	5	25	+	0110000000	4	+	0
				15	40	Same	Same	.....	0	25	+	0000000000	4	+	0
				21	20	Same	Same	.....	0	35	+	0000000000	4	+	0
				33	20	Same	Same	.....	3	30	+	0111000000	4	+	32---
				39	20	Same	Same	Imp.	0	25	±	0110000000	0	0	0
8	Tabes dorsalis.....	14 i.v., 14 i.m. 25 years ago. Irregular As and Bi. for past 5 years.	Penicillin (4,000,000)	0	0	.....	.....	.....	2	26	0	0000000000	4	+	0
				3	0	Imp.	Same	.....	6	26	0	0000000000	0	+	0
				6	0	Imp.	Same	.....	3	27	0	0000000000	4	+	0
				10	0	Imp.	Same	Same	0	24	0	0000000000	0	+	0
9	Tabes dorsalis (primary optic atrophy)	2 As and 25 Bi. 3 years ago.	Penicillin and malaria.	0	1	.....	.....	.....	0	41	2+	0000000000	4	+	3----
				8	±	Imp.	Same	.....	ND	ND	4+	0000000000	0	0	0
				16	1	Same	Same	.....	ND	ND	+	0011000000	4	+	0
				22	ND	Same	Same	Same	ND	ND	ND	ND	ND	ND	ND
10	Tabes dorsalis (primary optic atrophy)	"Shots" for 3 mo. 21 years ago. 1 i.v. and 1 i.m. each week for 1 year, ending 4 years ago. 1,400,000 u. penicillin 2 months ago.	Penicillin and malaria.	0	0	.....	.....	.....	5	36	0	0000000000	4	+	0
				End Rx	0	Same	Same	.....	3	27	0	1121000000	20	+	±----
				3	2	Imp.	Same	.....	1	28	0	0000000000	0	+	++---
				7	0	Same	Same	.....	0	30	ND	0000000000	0	+	0
				14	0	Same	KJ absent	.....	1	30	ND	0000000000	4	+	0
				26	0	Same	Same	Same	5	30	2+	0011000000	2	+	0
11	Tabes dorsalis (congenital).	29 As, 51 Bi., over 2 year period. Ending one year ago.	Penicillin and malaria.	−5	40	.....	.....	.....	ND	38	±	0000000000	4	+	ND
				0	3	.....	.....	.....	3	38	2+	0000000000	4	+	ND
				4	4	Same	Same	.....	1	20	3+	1111000000	20	+	ND
				12	ND	ND	ND	Worse	ND	ND	2+	0011000000	20	+	0

[1] Improved. [2] Not done. [3] Intramuscular. [4] Intravenous.

Ten of the eleven patients had subjective improvement and five had objective improvement. The only patient who did not show subjective improvement was the patient who had congenital syphilis and later developed tabes dorsalis.

One patient with paresis failed to show objective improvement and only one tabetic had improvement in the physical findings. No patient had become clinically worse.

In four cases the spinal fluid examination reverted to negativity, in five it was unchanged, and in two patients the serologic titer was higher than before treatment. No patient had developed active spinal fluid findings after treatment although in two cases (Nos. 7 and 8) there was an isolated increase in cell count.

If we exclude the four patients who had received therapy within 6 months of our spinal fluid examination, one finds that of the remaining seven, six had subjective improvement, three had objective improvement, and in two cases the spinal fluid reverted to negativity.

Discussion

Dattner, Thomas, and Wexler (*6*) state that while a normal cell count is the most reliable criteria in prognosticating the final outcome of a neurosyphilitic process, occasional progression may occur in the presence of a normal count. We agree with them that the cell count is the most reliable guide for determining the activity of neurosyphilis, but we also believe that the clinical progress must be evaluated. Patients who progress without an abnormal cell count must be rare. We have observed only one such case (No. 1) in approximately 800 cases of neurosyphilis. This was a 42-year-old white male who had an abnormal spinal fluid examination 3 years before we examined him. A large amount of aldarsone, trivalent arsenic, and bismuth had rendered the spinal fluid "inactive," but the paretic symptoms progressed. Nine months after treatment with penicillin and malaria, the spinal fluid examination was normal and the patient was much improved clinically. Dattner and Thomas (*1*) have pointed out that such a change may occur and that the "activity" of the spinal fluid should be determined at least 6 months after the termination of active antisyphilitic therapy. However, the rapid progression of this patient's symptoms and signs did not permit delay in starting additional therapy.

The fact that 10 of our 11 patients showed definite clinical improvement, that no patient became clinically worse, and that the spinal fluid examinations of more than one-third of them reverted

to negativity leads us to question the advisability of permitting these patients to remain without additional treatment for neurosyphilis. Periodic physical examinations and lumbar punctures are certainly indicated in the patients who are not treated, as well as in those who are.

The importance of careful consideration of therapy administered shortly before the finding of an inactive spinal fluid is demonstrated in the first patient. However, the clinical course was progressive in this patient, as well as the other three who had received recent treatment, and one was not justified in withholding additional treatment.

The results obtained by penicillin alone and penicillin and malaria are not significantly different. All five who received penicillin alone and five of six who received penicillin and malaria had clinical improvement, and two patients in each group developed negative spinal fluid examinations. Both of the patients who had a rise in Kahn titer received penicillin and malaria. It may well be that this represents only a fluctuating titer and is of no significance for the patient's well-being. It has been our experience that penicillin alone is adequate treatment for cases of neurosyphilis with "inactive" spinal fluids, and there is no necessity for subjecting them to the hazards of therapeutic malaria (*7*). This is probably also true when primary optic atrophy is present (*8*).

Summary and Conclusions

1. Eleven patients with neurosyphilis who met the criteria for a Dattner-Thomas formula in the spinal fluid examination have been treated with penicillin or penicillin and malaria and followed for 10 to 39 months. One of these had developed a rapid progression of paretic symptoms in the presence of "inactive" spinal fluid findings.

2. While the cell count and total protein, especially the former, are the most reliable criteria for determining the activity of neurosyphilis, progression of the disease may occur when both the cell count and total protein determination are within normal limits.

3. Treatment of our 11 patients resulted in clinical (objective and/or subjective) improvement in 10 cases, and 4 developed completely negative spinal fluid examinations.

4. If improvement after penicillin treatment of patients with central nervous system syphilis having the Dattner-Thomas formula shows such consistent change, one wonders whether it is valid. In view of the above findings the validity of withholding treatment in patients with inactive spinal fluids is open to question.

References

1. DATTNER, B.; THOMAS, E. W.: The management of neurosyphilis. Am. J. Syph. & Neurol., 26: 21, 1942.
2. DATTNER, B.; KAUFMAN, S. S.; THOMAS, E.: Penicillin in treatment of neurosyphilis. Arch. Neurol. & Psychiat., 58: 426, 1947.
3. DATTNER, B.: Evaluation of spinal fluid examinations. J. Ven. Dis. Inform., 29: 63, 1948.
4. DATTNER, B.; THOMAS, E. W.; WEXLER, G.: The Management of Neurosyphilis. Grune and Stratton, New York, 1944. P. 196.
5. CURTIS, A. C.; BURNS, R. E.; NORTON, D. H.: Neurosyphilis: Treatment with penicillin alone and with a combination of penicillin and malaria. Am. J. Syph., Gonor. & Ven. Dis., 31: 618, 1947.
6. DATTNER, B.; THOMAS, E. W.; WEXLER, G.: The Management of Neurosyphilis. Grune and Stratton, New York, 1944. P. 207.
7. CURTIS, A. C.; HORNE, S. F.; NORTON, D. H.: Neurosyphilis: Evaluation two years after treatment with penicillin and penicillin and malaria. (In press.)
8. CURTIS, A. C.; HORNE, S. F.; NORTON, D. H.: Treatment of syphilitic primary optic atrophy with penicillin and penicillin and malaria. (In press.)

Abstract of

The Jarisch-Herxheimer Reaction in Early Congenital Syphilis

A Study of 93 Patients Treated with Penicillin Alone [1]

Harold A. Tucker [2] and Osvaldo A. Pardo [3]

Between 1943 and March 1948, 93 children under 3 years of age were diagnosed as having untreated early congenital syphilis at the Johns Hopkins Hospital. Each was treated with penicillin as the sole antisyphilitic agent. A fever of 38° C. or greater in a previously afebrile patient, occurring from 4 to 36 hours after the start of penicillin administration, and lasting less than 36 hours, was interpreted as a febrile Jarisch-Herxheimer reaction. Forty-five children (48.5 percent) showed such reactions.

No relationship between incidence and magnitude of the reaction and age, race, sex, type of congenital syphilis, serologic titer or outcome was observed. The type of penicillin (e.g., amorphous or crystalline G) likewise did not appear to be a factor nor, within the range of 250 to 7,690 units/kg. of body weight, did the gravimetric dosage given. When it occurred, the reaction seemed to be entirely analogous to that seen in the adult with early acquired syphilis.

---

[1] From the U. S. Public Health Service and the Johns Hopkins Venereal Disease Research and Post-graduate Training Center, Baltimore 5, Md.

[2] Department of Bacteriology, University of Southern California School of Medicine, Los Angeles, California.

[3] Department of Dermatology and Syphilology, University of Habana, Cuba.

Five of the ninety-three children died and in each case prematurity, malnutrition, general debility, and/or intercurrent disease were complicating factors. None of these deaths was believed by us to be directly attributable to the Jarisch-Herxheimer reaction. It was our feeling that the outcome was largely dependent upon the general condition of the patient, and that a successful result depended as much or more, on general pediatric management as upon the type or amount of syphilotherapy employed.

Abstract of

An Attempt to Produce Aortic Lesions of Syphilis in Experimental Animals[1]

Fred A. Thompson and Harold J. Magnuson

In search for a more adequate measurement of the phenomena found in late syphilis, the production of cardiovascular syphilis in rabbits has been attempted. Two technics were employed in rabbits infected with the Nichols strain of *T. pallidum*. The first utilized supplemental cholesterol-cotton seed oil feedings, which regularly produced aortic and pulmonary artery plaque-like lesions. The second depended on the development of hypertension secondary to renal ischemia, produced by cellophane wrapped around both kidneys. This method produced aortic lesions with actual aneurysm formation. However, lesions have occurred with equal frequency in the syphilitic and nonsyphilitic animals and there is as yet no evidence that any of these lesions are syphilitic.

[1] From the Syphilis Experimental Laboratory, U. S. Public Health Service, University of North Carolina, Chapel Hill, North Carolina. Aided in part by a Research Grant of the Research Grants Division, National Institutes of Health, U. S. Public Health Service.

Experimental Mouse Syphilis

II. Minimal Infectious Number of *Treponema Pallidum* [1]

Paul D. Rosahn and Catherine L. Rowe

Careful observers (*1*) have reported that the intratesticular inoculation of one to two spirochetes regularly produces syphilitic lesions in the rabbit. Experiments subsequently conducted in this laboratory have confirmed these findings. In a consideration of the problem of syphilis in the mouse, it seemed desirable to determine in similar manner the minimal number of treponemes capable of initiating mouse infection.

The problem here is considerably more complex than that presented by comparable studies in the rabbit. The rabbit, if inoculated intratesticularly with pathogenic organisms, invariably develops a lesion richly suffused with treponemes, and the fact of infection can be determined directly by darkfield examination of the lesion. The mouse, on the other hand, has never been observed in repeatable experiments to develop specific lesions after inoculation (*2*). Because of the absence of focal tissue reactions, syphilitic infection in the mouse can be determined with certainty only by subinoculation of its tissues into a test animal of another species, the rabbit. The subsequent development of a treponeme-bearing lesion in the test rabbit is for practical purposes the sole evidence that can be adduced to indicate that infection of the primary mouse host has occurred. As a result of the complete absence of tissue reactivity in the mouse, any attempt to determine the effectiveness of graded inocula in producing infection must give consideration to the period of residence of the inoculated treponemes in the mouse, i.e., the time elapsing between mouse inoculation and the transfer of mouse tissue to the test rabbit. This variable of time is not a complicating factor in studying the effect of inocula containing different numbers of treponemes on the initiation of syphilitic infection in the rabbit.

Material and Methods

Animals

The mice were all adult males of the white hybrid "Swiss" type. The rabbits represented a variety of mixed breeds, all males, weighing from 2.0 to 3.3 kg. at the time of inoculation.

[1] From the laboratories of the New Britain (Conn.) General Hospital. Aided by a grant from the Research Grants and Fellowships Division, National Institutes of Health.

Housing and Feed

All mice were segregated in individual compartments, two to a cage. They received commercial food pellets and a free supply of water. Rabbits were housed in individual cages. They were fed commercial food pellets and liberal amounts of water. The temperature of the animal rooms was thermostatically regulated at 65° to 70° C.

Inoculum

The Nichols strain of *Treponema pallidum* was utilized throughout. Active testicular lesions from routine passage rabbits were excised, minced, and ground in a mortar with physiological saline. Enumeration of the treponemes was performed according to the technic of Magnuson, Eagle, and Fleischman (*1*), with two minor variations: (1) supernatant fluid for counts and inoculum was obtained by sedimentation instead of by certifugalization, and (2) counts were made with 0.01 cc. of the supernatant fluid instead of with 0.02 cc. The limits of error of these counts were calculated to be within the range described by Magnuson and his associates. Serial dilutions of the standardized emulsions were then prepared with saline.

Animal Inoculation

Groups of mice were inoculated intraperitoneally with 0.2 cc. of the different dilutions of the original emulsion. Two series of mice were inoculated. In the first experiment, begun on May 13, 1948, lymph node transfers from mouse to rabbit as a test of mouse infection were made 11 to 13 days and 81 to 82 days after the mice were inoculated. In the second experiment, begun on September 21, 1948, rabbits were subinoculated with mouse lymph nodes 10 days and 90 to 92 days after intraperitoneal infection of the mice. All rabbit tests of mouse infection were conducted as follows: The mouse was sacrificed, and all available lymph nodes, including the inguinal, periaortic, axillary, and subclavian groups were excised. The nodes were then pooled, ground in a mortar with 1 cc. of saline, and the entire emulsion inoculated into the right and left testicles of a single test rabbit. All test rabbits were observed by frequent clinical examinations for 70 days following intratesticular inoculation. Clinically suspicious lesions were subjected to dark-field scrutiny, and if this revealed treponemes, the mouse from which the rabbit inoculum was derived was considered to have been infected.

Results

The accompanying table summarizes the results obtained in the two experiments. The findings are fairly consistent within each experiment and also between them. When the rabbit test to determine infection in the mouse was conducted in from 10 to 13 days following intraperitoneal inoculation of the mice with graded inocula of treponemes, none of the 32 mice receiving from 25,000 to 500,000 organisms were shown to have been infected, and only 7 of 15 mice inoculated with from 1 to 5 million organisms were demonstrably infected. In contrast to these findings were those noted when the rabbit test was made 81 to 92 days after the mice were inoculated. At this time interval 14 of the 15 mice inoculated with 250,000 to 5 million organisms gave evidence of infection, while infection was absent in all of 7 mice receiving inocula containing 25,000 to 50,000 organisms. When the rabbit test was performed 10 to 13 days after mouse inoculation, 1 million organisms in the mouse inoculum was the smallest number producing mouse infection. After 81 to 92 days had elapsed from the time of mouse inoculation to the rabbit test of infection, 100,000 organisms were shown to be capable of establishing an infection in the mouse.

Table 1.—*The minimal infectious number of* T. pallidum *in experimental mouse syphilis. Proportion of positive results in rabbits, related to duration of mouse infection*

Experiment No.	Number of inoculated organisms	Duration of mouse infection	
		10 to 13 days	81 to 92 days
	+000		
1	5,000	[1] 3/6	4/4
1	1,000	2/5	2/2
2	1,000	2/4	5/5
1	500	0/4	0/1
1	250	0/6	3/3
2	200	0/4	1/3
1	125	0/6	1/3
2	100	0/4	1/5
2	50	0/4	0/4
2	25	0/4	0/3

[1] The denominator of all fractions indicates the number of mice tested, and the numerator the number of positive mice.

Discussion

These experiments utilized a method for determining infection in the mouse, by transfer of its lymph nodes to a test rabbit, which is based on previous experience (*3*). This showed that of all

organs examined, lymph nodes gave the highest proportion—approaching 100 percent—of positive lesions in subinoculated rabbits. Nevertheless, a mouse with lymph nodes noninfectious for rabbits might conceivably harbor the infectious agent of syphilis in organs other than lymph nodes, such as blood, spleen, or skin. These other organs were not tested. Attention should also be directed to our use of the intraperitoneal route of mouse inoculation. The results with graded inocula introduced into the peritoneal cavity were not checked by parallel experiments utilizing subcutaneous or intravenous inoculations. Furthermore, the test rabbits were observed for only 70 days before terminating the experiment, because in our previous experience an incubation period in the rabbit in excess of 70 days occurred only once out of 91 different positive lymph node subinoculations. Bearing all of these qualifications in mind, the title of this report might best be amplified for precise purposes to the following descriptive designation: "The minimal infectious number of treponemes in experimental mouse syphilis, after intraperitoneal inoculation of graded dilutions of the Nichols strain of organism, the determination of infection in the mouse being based on the development of a treponeme-bearing lesion in the rabbit testes following subinoculation with the excised mouse lymph nodes, the rabbit being observed for seventy days."

After intraperitoneal inoculation of treponemes they invade the blood stream of the mouse and lodge in various organs, including lymph nodes. Their ultimate fate is unknown. How long after the intraperitoneal inoculation do the treponemes in the original inoculum continue to migrate and invade various mouse organs? Is their rate of multiplication equal to, less than, or greater than their rate of dissolution? Is there any alteration in their pathogenicity with long residence in the mouse tissues? Do they lie dormant, in a hibernating nonreproducing state, or do they divide and multiply? The experiments described herein do not answer all these questions, but they may have some bearing on one or two of them.

When lymph nodes from inoculated mice were subinoculated into rabbits after an incubation period of 10 to 13 days, positive rabbit lesions occurred only when the original mouse inoculum contained not fewer than 1 million organisms. The proportion of positive results was approximately 50 percent with mouse inocula of 1 to 5 million organisms. When the incubation period in the mouse was extended to 81 to 92 days before lymph node transfer to rabbits, positive results in the rabbit were 100 percent with original mouse inocula of 1 million to 5 million organisms, and lesions developed

with lymph nodes from mice receiving 100,000 organisms in the inoculum.

Increasing the incubation period in the mouse by 70 to 80 days resulted in a tenfold decrease in the number of organisms in the original mouse inoculum necessary to produce lesions in rabbits on transfer of mouse nodes. If after 10 days of incubation in the mouse, the minimal number of inoculated organisms required to demonstrate infection was 1 million, and after 90 days it was 100,000 organisms, it appears reasonable to deduce that a tenfold numerical increase occurred in the 80-day interval between these limits. This deduction may have merit only provided the assumption is made that all the organisms reaching the nodes from the original inoculum were already present within them 10 days after inoculation, and further, that there was no change in the virulence of these organisms during their period of residence in the nodes. If these assumptions are correct, and each treponeme on reaching the tissue divides into two organisms, then it can be concluded that in the mouse there are 3.3 divisions in 80 days, or 1 division each 24 days ($2^{3.3} = 10$, $80/3.3 = 24.3$). It is readily admitted that this conclusion is based on tenuous assumptions which further work may demonstrate to be false. Studies now under way may help to clarify the problem.

Magnuson, Eagle, and Fleischman (*1*) have estimated the division time for *T. pallidum* in rabbits to be on the order of 30 hours. The experiments described in the present report suggest that in the mouse, provided certain basic assumptions are correct, the division time of treponemes is approximately 24 days. If further observations confirm this estimate, we have here a fundamental difference between the mouse and rabbit hosts which may have a significant bearing on their differing reactions to syphilitic infection.

Summary

1. Groups of mice were inoculated intraperitoneally with graded dilutions of *T. pallidum* varying from 25,000 to 5 million organisms. Following incubation periods in the mice of 10 to 13 days and of 81 to 92 days, lymph nodes from the inoculated mice were subinoculated intratesticularly into rabbits.

2. The minimal number of organisms in the original inoculum capable of producing lesions in rabbits at 10 to 13 days following mouse inoculation, was 1 million. The comparable value at 81 to 92 days after mouse inoculation was 100,000 organisms, a tenfold difference.

3. It was suggested that provided certain assumptions are operative, this difference indicates a division time of *T. pallidum* in the mouse of approximately 24 days. This prolonged division time, in contrast to the 30-hour division time in the rabbit as estimated by Magnuson, Eagle, and Fleischman, may possibly account, at least in part, for the differing reactions of mouse and rabbit to syphilitic infection.

References

1. Magnuson, H. J.; Eagle, H.; Fleischman, R.: The minimal infectious inoculum of *Spirochaeta pallida* (Nichols strain), and a consideration of its rate of multiplication in vivo. Am. J. Syph., Gonor. & Ven. Dis., 32: 1–18, 1948.
2. Gueft, B.; Rosahn, P. D.: Experimental mouse syphilis, a review of the literature. Ibid., 32: 59–88, 1948.
3. Rosahn, P. D.; Gueft, B.; Rowe, C.: Experimental mouse syphilis. I. Organ distribution of the infectious agent. Ibid., 32: 327–336, 1948.

The Application of Studies of the Growth Requirements of *Neisseria Gonorrhoeae* and of *Hemophilus Ducreyi* to the Improvement of Methods for the Isolation of These Organisms from Clinical Material[1]

J. H. Hill, E. E. Nell, and A. M. Mueller

Introduction

These studies are part of an investigation of the chemical growth requirements of *Neisseria gonorrhoeae* and of *Hemophilus ducreyi,* for the purpose of determining the fundamental biology of these organisms and of applying the results to the improvement and simplification of media for their isolation from clinical material. In regard to the gonococcus, the media commonly employed in the United States are prohibitive in many other countries, and satisfactory substitutes must be found. With *H. ducreyi,* not only are simple methods for its isolation lacking, but the very characteristics for its identification remain to be determined This can be done only on the basis of further investigation of its biologic behavior.

[1] From the U. S. Public Health Service and the Department of Bacteriology of the Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Md.

The results reported here on the gonococcus consist of three groups of experiments:

A. An investigation of the nutritive and toxic ranges of protein hydrolysates.
B. The effect of certain other substances upon growth of the organism.
C. The effect of modifications of media for the isolation of the gonococcus from clinical material.

The experiments with *H. ducreyi* concern observations on the growth of the organism in a number of experimental media.

Part I

The Gonococcus

A. Experiments with Protein Hydrolysates

No controlled data can be found that establish the superiority of any given protein hydrolysate or "peptone" for growth of the gonococcus, nor that determine the optimal and toxic concentrations of such substances. Although there is an increasing bibliography, such as the recent report of Schuhardt, Rode, Foster and Oglesby (*1*) on the toxic effects of peptones on other organisms, no such information is available for the gonococcus, except the early study of McLeod, Wheatley, and Phelon (*2*) on the toxic effect of certain amino acids, and the valuable report of McLeod (*3*) on the effect of peptone on viability.

We have therefore determined the optimal and toxic concentrations of 39 protein hydrolysates. The method has consisted of the incorporation of the hydrolysates in a nonnutrient base, which is the Medium B of Gould, Kane, and Mueller (*4*) with glutamic acid and histidine omitted. The hydrogen ion concentration was adjusted to 7.3 after addition of the hydrolysates in concentrations from 0.01 through 5 percent. The plates were streaked with suspensions of 18-hour chocolate agar slants of freshly isolated strains of gonococci, washed 4 times in the basic medium without agar, incubated in 10-percent carbon dioxide for 48 hours, and examined for the amount and quality of growth. The minimal optimal concentration of hydrolysate was taken as the smallest amount which permitted the growth of 90 percent or more of the strains. The minimal toxic concentration was the first one showing less growth after the optimal concentrations. Three lots of all commonly used hydrolysates were tested whenever possible and at least 16 strains of gonococci were used, often many more. The results are shown in table 1.

It is shown by this table that all of the 32 hydrolysates tested,

Table 1.—*Minimal optimal and toxic concentrations of 32 protein hydrolysates*

Hydrolysate	Minimal optimal concentration	Minimal toxic concentration
	Percent	*Percent*
Armour peptone siccum	0.05	2.0
Blood hydrolysate [1]	.05	1.0
Blood (whole) hydrolysate [1]	.05	.5
N–Z Case [2]	.05	4.0
N–Z Amine, type A [2]	.05	1.0
N–Z Amine, type B [2]	.05	2.0
Peptonized milk [3]	.05	.5
Plasma hydrolysate [1]	.05	1.0
Proteose peptone [3]	.05	2.0
Proteose peptone No. 2 [3]	.05	1.0
Proteose peptone No. 4 [3]	.05	.5
Thiotone [4]	.05	2.0
Wilson peptone	.05	2.0
Casamino acids, tech. [3]	.1	2.0
Casamino acids, vitamin-free [3]	.1	1.0
Casein hydrolysate, enzyme [5]	.1	.5
Casitone [3]	.1	2.0
Edamin [2]	.1	.5
Lactalysate [4]	.1	1.0
Myosate [4]	.1	2.0
Neopeptone [3]	.1	2.0
Phytone [4]	.1	1.0
Polypeptone [4]	.1	3.0
Proteose peptone No. 3 [3]	.1	3 0
Protone, [3]	.1	4.0
Witte peptone	.1	2.0
Bacto peptone [3]	.5	3.0
Casamino acids [3]	.5	2.0
Casein hydrolysate [5]	.5	2.0
Gelysate [4]	.5	[6] 5
Trypticase [4]	.5	3.0
Tryptone [3]	.5	1.0

[1] Baxter.
[2] Sheffield.
[3] Difco.
[4] Baltimore Biological Laboratory.
[5] National Biochemical Corporation.
[6] Above.

with which optimal growth was obtained, reached this level in a concentration of not more than 0.5 percent, instead of the 1.5 or 2 percent usually recommended. Thirteen of the thirty-two hydrolysates were optimal under the conditions of this test at as low as 0.05 percent, the same number were optimal at 0.1 percent, while only 6 required 0.5 percent for optimal growth. In regard to toxicity, 5 showed a diminution of growth at as low as 0.5 percent, 8 were toxic at 1 percent, 12 at 2 percent, and 7 were not toxic except at concentrations of more than 2 percent.

Optimal growth was not reached with the following seven hydrolysates in concentrations of from 0.01 through 5.0 percent:

casein acid hydrolysate,[2] lactalbumin hydrolysate,[2] Arlington peptone, Arlington peptone, biuret-free, Arlington peptone "mixed substrate," soy protein hydrolysate[2] and tryptose.[3]

It is evident from these experiments that many protein hydrolysates are suitable for the growth of the gonococcus, that no one substance can be selected as superior, and that, as will be confirmed under section C below, smaller amounts of the hydrolysates may be employed than are usually recommended.

B. The Effect of Certain Adjuvants upon Growth of the Gonococcus

Although the use of such adjuvants as hemoglobin, yeast, or liver preparations have been of proved value for growth of the gonococcus, no quantitative comparisons of them are available nor have they been studied except in nutrient media. It seemed important to determine quantitatively their effect when present as the sole sources of nutriment. The method employed was the same as described in the previous section. The results are shown in table 2.

Table 2.—*The effect of hemoglobin, liver, and yeast preparations on growth of the gonococcus in a nonnutrient base*

Substance	Minimal optimal percent
Hemoglobin, Difco	0.00195
Hemoglobin, Pfansteil	.06250
Bacto liver, Difco	[1]
Liver fraction "L," National Biochemical Corporation	.05
Yeast extract, Baltimore Biological Laboratory	.01
Yeast extract, Difco	.05
Autolyzed yeast, Difco	[1]
Supplement B, Difco, not autoclaved	.5
Supplement B, Difco, autoclaved	1.0
Yeast hydrolysate, National Biochemical Corporation	.1

[1] Not reached.

It is of interest that, with the exception of Supplement B, and the yeast hydrolysate, all of the active substances in the group were effective at levels of 0.05 percent or less, and can in themselves support growth of the gonococcus.

The findings with hemoglobin suggest that not only is the heme important, but that the organism may be able to use the amino acids present in the molecule.

[2] National Biochemical Corp.
[3] Difco.

The difference in activity of the two liver products studied is striking and indicates the need for further investigation of the liver fraction "L."

It should be noted that the Difco yeast extract, optimal at 50 mg. percent is prepared from autolyzed yeast, which was ineffective.

These findings, as confirmed in section C, suggest that in the presence of optimal amounts of one or more of these "adjuvants," the use of protein hydrolysates may be unnecessary.

C. Media Variations as Shown with Strain-by-Strain Comparisons of Growth of the Gonococcus from Clinical Specimens

These findings are summarized in table 3, from which the following conclusions are drawn:

1. The Bacto-G C Base with hemoglobin and Supplement B gives about 10 percent more recoveries of the gonococcus than are obtained on the Bacto-Proteose No. 3 agar with hemoglobin and Supplement A. In addition it may be noted that of the 236 strains used in these series, i.e., growing on one or more of the test media, 227, or 96.2 percent, grew on the G C base with hemoglobin and Supplement B. The superiority of the G C base medium indicates that the findings from laboratories using only the older medium are about 10 percent lower than indicated. Allowance for this fact should be made in the evaluation of clinical results based upon the use of the older medium.

2. While the omission of peptone from the G C base medium has given results slightly inferior to the use of 1.5 percent peptone, reduction of the amount of peptone to 0.5 percent has so far been as good as the use of three times that amount.

3. Autoclaving the Supplement B has yielded as many recoveries of the gonococcus as has the addition of the supplement after autoclaving.

4. The substitution of 0.5 or 0.1 percent Bacto Yeast Extract has so far given results inferior to the use of Supplement B.

5. The inclusion of 50 mg. percent of cystine in the G C Base medium was toxic, and no improvement was found by the addition of 10 or 25 mg. percent of cystine. This emphasizes the fact that the value of cystine must be determined for every medium in which it is used.

6. The addition of glutathione and soluble starch gave results at least as good as the unmodified G C base medium and suggests that the study of other quantitative variations of these adjuvants may be of value.

Table 3.—*Strain-by-strain media comparisons of growth of the gonococcus from clinical specimens*

Number	Medium			Total	Positive	
	Base	Peptone	Supplement		Number	Percent
1	Bacto-G C Base	1.5 Percent proteose No. 3	Supplement B	124	120	96.8
2	Bacto Proteose No. 3 agar	2 Percent proteose No. 3	Supplement A	124	108	87.1
1	Bacto-G C Base	1.5 Percent proteose No. 3	Supplement B	37	36	97.3
3	do	0.5 Percent proteose No. 3	do	37	37	100
1	do	1.5 Percent proteose No. 3	do	73	71	97.3
4	do	0	do	73	69	94.5
1	do	1.5 Percent proteose No. 3	do	54	50	92.6
5	do	1.5 Percent proteose No. 3	do B, autoclaved	54	50	92.6
1	do	1.5 Percent proteose No. 3	do	54	50	92.6
6	do	1.5 Percent proteose No. 3	do Glutathione, 15 mg. per liter Soluble starch, 3 gm. per liter	54	51	94.4
1	do	1.5 Percent proteose No. 3	Supplement B	8	8	100
7	do	1.5 Percent proteose No. 3	Supplement B, cystine, 50 mg. percent	8	3	37.5
1	do	1.5 Percent proteose No. 3	Supplement B	15	14	93.3
8	do	1.5 Percent proteose No. 3	Supplement B, cystine 25 mg. percent	15	13	86.7
1	do	1.5 Percent proteose No. 3	Supplement B	24	24	100
9	do	1.5 Percent proteose No. 3	Supplement B, cystine 10 mg. percent	24	24	100
1	do	1.5 Percent proteose No. 3	Supplement B	27	26	96.3
10	do	1.5 Percent proteose No. 3	0.1 Bacto yeast extract, autoclaved	27	23	85.2
1	do	1.5 Percent proteose No. 3	Supplement B	58	54	93.1
11	do	1.5 Percent proteose No. 3	0.5 Bacto yeast extract, autoclaved	58	44	75.9

Part II

Hemophilus Ducreyi

Even the classification of this organism is controversial; Bergey's Manual (*5*) places it in the genus *Hemophilus*, while the British, Topley and Wilson (*6*) question the validity of this step. Means for the easy isolation of the organism from clinical material are lacking, as well as methods for its accurate identification and differentiation from similar forms.

While Lwoff and Pirosky (*7*) showed that in a nutrient base the old strains they studied required the X factor, or hemin, but not the V factor, di- or triphosphopyridine nucleotide, further work is clearly needed in regard to the essential growth requirements of *H. ducreyi.*

Two methods have been used in this study. The first, using plating methods, was abandoned because of the difficulty of freeing the bacterial suspensions sufficiently from growth factors carried over from the medium. The second method obviated this difficulty and has consisted of the inoculation of liquid media with suspensions, followed by plating after 48 hours of incubation in 10 percent carbon dioxide. The experiments are summarized in table 4.

It is evident from this table that the addition of hemin did not permit growth in either the base or in infusion broth, so that it may be concluded that under these conditions other factors than hemin are essential. While the addition of serum to the nonnutrient base gave no growth, or a trace, when serum was added to the infusion base, heavy growth was obtained. Some factor, present in the infusion broth, is therefore required for growth. This factor does not appear to be either glutamine or hemin. The addition of hemoglobin to the nonnutrient base gave slight growth, while in infusion broth heavy growth was obtained with hemoglobin. It should be added here that the addition of 0.5 percent Thiotone did not improve the findings in the nonnutrient base, with or without the addition of serum, glutamine, hemin, or glutamine and hemin. The amino acids present in hemoglobin did not permit growth.

General Conclusions

1. A comparison of protein hydrolysates has shown that, under the conditions of these experiments, no one peptone can be considered as superior for growth of the gonococcus.

2. The hydrolysates reach their optimal levels for growth at

Table 4.—*Experiments with* Hemophilus ducreyi

Medium	Adjuvant		Findings
	Substance	Percent	
Base	0		No growth.
Do	Serum or plasma	10	0 to trace.
Do	Whole blood	10	Good growth.
Do	Hemin	.01	No growth.
Do	Hemoglobin	.20	Slight growth.
Do	Glutamine	.01	No growth.
Do	Plasma	10	No growth.
Do	Glutamine	.01	
Do	Hemin	.01	No growth.
Do	Glutamine	.01	
Do	Plasma	10	0 to scant growth.
Do	Hemin	.01	
Do	Liver fraction "L"	.05	No growth.
Do	Serum	10	Slight growth.
Do	Liver fraction "L"	.05	
Do	Supplement B	1.0	No growth.
Do	Supplement B	1.0	No growth.
Do	Hemin	.01	
Do	Supplement B	1.0	No growth.
Do	Liver fraction "L"	.05	
Infusion broth	0		No growth.
Do	Hemin	.01	No growth.
Do	Serum	10	Heavy growth.
Do	Serum	10	Heavy growth.
Do	Hemin	.01	
Do	Hemoglobin	.2	Heavy growth.
Do	Whole blood	10	Heavy growth.

0.05, 0.1, and 0.5 percent, rather than at the 1.5 or 2 percent usually recommended for use.

3. Except for 7 of 32 hydrolysates found of value, they became toxic at concentrations of 0.5, 1, and 2 percent.

4. The ability of small amounts of hemoglobin, certain yeast preparations, and of liver fraction "L" to support the growth of the gonococcus when added to a nonnutrient base has been shown.

5. The favorable effect of substitution of the G C base medium for the Proteose No. 3 agar medium has been confirmed in clinical isolations.

6. The possibility of reducing the amount of peptone in media has been shown by a comparative series of clinical isolations.

7. In regard to *H. ducreyi,* the X factor, hemin, has not been found adequate to permit growth of the organism.

8. Some factor, apparently not glutamine, and not hemin, is present in infusion broth, which permits the growth of *H. ducreyi,* with serum or hemoglobin, neither of which alone is adequate to permit heavy growth, when added to a nonnutrient base.

References

1 Schuhardt, V. T.; Rode, L. J.; Foster, J. W.; Oglesby, G.: An anti-brucella factor in peptones. J. Bact., 57: 1, 1949.
2. McLeod, J. W.; Wheatley, B.; Phelon, H. V.: On some of the unexplained difficulties met with in cultivating the gonococcus. Brit. J. Exper. Path., 8: 25, 1927.
3. McLeod, J. W.: Smear and culture diagnosis in gonorrhea. Brit. J. Ven. Dis., 23: 53, 1947.
4. Gould, R. G.; Kane, L. W.; Mueller, J. H.: On the growth requirements of *Neisseria gonorrhoeae*. J. Bact. 47: 287, 1944.
5. Breed, R. S.; Murray, E. G. D.; Hitchens, A. P.: Bergey's Manual of Determinative Bacteriology. Sixth Edition. The Williams and Wilkins Co., Baltimore, 1948. P. 584.
6. Wilson, G. S.; Miles, A. A.: Topley and Wilson's Principles of Bacteriology and Immunity. 3rd Edition. Revised. The Williams and Wilkins Co., Baltimore, 1: 786, 1946.
7. Lwoff, A.; Pirosky, I.: Détermination du Facteur de Croissance pour Haemophilus Ducreyi. Comptes. Rend. Soc. de Biol. 124: 1169, 1937.
8. Difco Manual. Eighth Edition. Detroit, 1948. P. 179.

Studies on Some Characteristics of the Pleuropneumonia Group of Organisms[1]

M. H. Hatch

Twenty-six isolations of pleuropneumonia-like organisms (PPLO) have been made from the genital tract of individuals visiting a venereal disease clinic. Twenty-four of sixty-one (39.3 percent) female cervical cultures and two of six (33.0 percent) male urethral cultures were positive for PPLO. The organisms were isolated on Difco beef heart infusion agar, pH 7.8, with 20 percent human ascitic fluid and 10 units per milliliter of penicillin. Control plates without penicillin were run to exclude the possibility of production of pleuropneumonia-like forms from other bacteria in the presence of penicillin; these control plates showed PPLO in all except three instances. The organisms isolated from humans resemble other PPLO (rat, mouse, and streptobacillary "variant") in colony form, slow rate of growth, slight growth in fluid media, and requirement for serum or ascitic fluid in the medium. Best growth has been obtained with fresh beef heart infusion media, pH 7.8, with 10-percent horse serum.

Early in this work a method was sought to preserve PPLO so that reserves of strains could be maintained essentially un-

[1] From the School of Hygiene and Public Health, the Johns Hopkins University, Baltimore, Md.

changed. Lyophilization of broth cultures did not yield a satisfactory number of recoveries upon reconstitution. The method finally adopted consists of cutting a block of agar with colonies from a plate, sealing the block within a Pyrex serologic tube with a hot flame, freezing rapidly by immersing the tube in a dry-ice-alcohol mixture, and storing in a dry-ice chest. To achieve recovery the block is thawed rapidly in a 37° C. water bath, removed from the tube, and streaked across a fresh serum agar plate. This technic is simple and has proved very efficient; PPLO can be recovered after storage in this manner for at least 6 months.

Antibiotic sensitivity experiments have been run using eight strains of PPLO from different sources (L1 from *Streptobacillus moniliformis*, L3 from the rat, L5 from the mouse, and five human genital strains). These tests have all been done on beef heart infusion agar plates, pH 7.8, with 10 percent bovine serum, containing varying concentrations of the following antibiotics: Penicillin, streptomycin, bacitracin, aureomycin, polymyxin, and tyrothricin. Plates were read at 2 and 7 days; the 7-day results are given. Penicillin, polymyxin, and bacitracin failed to inhibit growth of any of the eight strains in concentrations as high as 500 units, 50 micrograms, and 200 units per milliliter medium, respectively. Streptomycin completely inhibited growth of all five human strains in a concentration of 25 micrograms per milliliter medium, but not in a concentration of 12.5 micrograms per milliliter. The mouse and rat strains were resistant to 50 micrograms streptomycin per milliliter. Aureomycin completely inhibited growth of seven of eight strains in a concentration of 50 micrograms per milliliter medium, but not in a concentration of 25 micrograms per milliliter. The human strains appeared more resistant than the mouse and rat strains. Tyrothricin completely inhibited growth of seven of eight strains in a concentration of 3.1 micrograms per milliliter medium, but not in a concentration of 1.5 micrograms per milliliter. Again the human strains were more resistant. The PPLO studied seem to have a higher in vitro order of resistance to these antibiotics than do most bacteria.

Attempts have been made to study the immunological relationships among these organisms. Antiserums have been produced in rabbits which show complement-fixing and agglutinating antibodies. The complement-fixation reaction has indicated the presence of antibodies in the antiserums to the medium in which the organisms were grown for immunizing antigens. This possibility seems to have been overlooked in previous immunologic studies on PPLO, but modern immunochemists dislike the use of such antiserums. Attempts to extract a carbohydrate antigen from

the organisms, using the formamide technic, for use in precipitin tests have failed. Good immunologic analysis awaits the development of a technic for growing these organisms in quantity on a medium free from antigenic constituents.

Since the stumbling block in laboratory work with PPLO (serologic work, for instance) is in the paucity of their growth and in the necessity for using highly complex, natural media, it is felt that studies on the nutritional requirements of PPLO are of prime importance. With this in mind work is in progress attempting to define the components of serum necessary to support their growth and to simplify or replace the infusion base.

Aureomycin in the Treatment of Granuloma Inguinale[1]

Raymond C. V. Robinson, DuMont F. Elmendorf, Jr., and Harold E. C. Zheutlin

The possible therapeutic efficacy of aureomycin in granuloma inguinale was verbally advanced by Wright, Sanders, and their co-workers (*1*) in the presentation of a subsequently published paper (*2*). These authors, primarily interested in the effect of the drug on lymphogranuloma venereum, treated three patients in whom a diagnosis of granuloma inguinale had been made. Although the posttreatment observation period in their cases was insufficient to permit definite conclusions, the clinical response was such as to warrant further study.

Recently Greenblatt and co-workers (*3*) reported oral aureomycin to be effective in the treatment of four patients with streptomycin-resistant granuloma inguinale. These patients were followed only a short time and the final clinical outcome is not known.

We have therefore attempted a more adequate evaluation of aureomycin in granuloma inguinale, using patient material available at the Baltimore Rapid Treatment center.[2]

---

[1] From the Venereal Disease Division of the Medical Clinic, Johns Hopkins Hospital and University, Baltimore, Md.

Aureomycin was furnished through the courtesy of Lederle Laboratories Division, American Cyanamid Co.

This work was supported by a grant-in-aid from the Research Grants and Fellowships Division, National Institutes of Health, U. S. Public Health Service.

[2] Baltimore City Hospitals.

From July 1, 1948, to March 15, 1949, 42 patients with proved granuloma inguinale were treated with various treatment schedules, using either the oral or intramuscular route of administration. Although no one schedule has been evolved as yet which might be recommended as superior, the observations and conclusions are of sufficient interest to justify a preliminary report.

Only those patients were accepted for study whose lesions were found to contain *Donovania granulomatis* in stained scrapings or smears. There was no selection of cases based on factors such as previous treatment, duration of infection, or extent of involvement.

Certain clinical manifestations observed in this series of patients differed from those reported by others. Greenblatt (*4*) has stated that "the lesion commonly presents itself as a rising or swelling (bubo) in the groin." In our series, however, the granulomatous lesions began, in every case, on the external genitalia or in the perianal region. Kornblith (*5*) has claimed that in all cases of granuloma inguinale the regional lymphatics are involved. Regional lymphadenopathy was not observed in our cases, except in the presence of frank secondary pyogenic infection. Oral lesions were observed in one patient. In no case was osseous or visceral involvement detected.

Subsequent to hospitalization and treatment in the rapid treatment center, each patient was instructed to report to the Venereal Disease Clinic of the Johns Hopkins Hospital for observation at weekly intervals for the first month and then at monthly intervals for one year. Fourteen patients kept no appointments. The remaining 28 have been followed for periods varying up to 165 days.

Seven treatment schedules were employed as described below. The smaller dosages of the drug given in schedule one, were similar to those used by Wright, Sanders, and their associates (*2*). Because of early failures in our series on this schedule we decided, when the drug became more readily available, to use larger amounts.

Four patients were treated with single daily intramuscuular injections of aureomycin for periods ranging from 23 to 31 days (table 1). The aureomycin was dissolved in distilled water immediately prior to each administration.

One patient (case 4), who had suffered from granuloma inguinale for 6 years and who had received 284 injections of tartar emetic in the past, showed no beneficial effects after 23 days of aureomycin therapy, and the drug was discontinued. This patient failed to return for further observation or treatment. One patient (case 2) failed to return to the clinic after discharge from

Table 1.—*Granuloma inguinale treated with 20 mg. of aureomycin intramuscularly once a day*

Case No.	History No.	Duration of disease	Previous treatment	Duration of treatment (days)	Total dose of aureomycin (gm.)	Clinical result	Total period of post-treatment observation (days)
1	J.H.H. 472652	2 to 3 months	None	25	0.50	Cure [1]	30
2	B.C.H. 121737	6 months	do	30	.60	Failure [2]	0
3	J.H.H. 473347	6 months	Tartar emetic	31	.61	Relapse [3]	23
4	B.C.H. 121623	6 years	do	23	.46	Failure	0

[1] Cure: Lesion healed.

[2] Failure: No obvious response.

[3] Relapse: Partial or complete healing followed by subsequent reappearance of or increase in size of lesion.

the hospital. He gave a history of lesions present for 6 months. At the end of 30 days of treatment there was no visible evidence of healing, although there was relief of pain.

Of the other two persons treated on this schedule, one (case 1) showed complete epithelialization 30 days after discharge and is considered a 30-day "cure"; the other patient (case 3) relapsed 23 days after completion of the course of aureomycin.

Since the dosage of the first schedule was obviously inadequate, and since the drug by this time had been made available in 100-mg. capsules, the next 10 patients were treated with aureomycin orally, 100 mg. 3 times daily before meals for periods varying from 13 to 30 days (table 2). The total dosage ranged from 4.1 to 10.0 gm.

One patient (case 5), who received 10 gm., showed no demonstrable effect and is classified as a failure. Another patient (case 6), whose lesions involuted, was followed only 14 days and is recorded as a questionable cure. A third patient (case 7) who failed to show improvement after 14 days following completion of therapy is considered a failure.

Of the remaining 7 patients, who were observed 30 days after completion of treatment, the lesions in 5 (cases 8, 9, 10, 11 and 14) had completely healed, and 2 (cases 12 and 13) showed definite improvement. These last 2 patients, after observation periods of 39 and 44 days, respectively, were not progressing satisfactorily and are classified as relapses after partial healing. Four (cases 8 to 11, inclusive) of the 5 patients observed to be "cured" at the end of 30 days were subsequently found to demonstrate activity at the site of previous lesions and are recorded as relapses after periods of 35, 38, 41, and 58 days. Of the 10 patients in this group, only

Table 2.—*Granuloma inguinale treated with 100 mg. of aureomycin orally three times a day*

Case No.	History No. J.H.H.	Duration of disease	Previous treatment	Duration of treatment (days)	Total dose of aureomycin (gm.)	Clinical result	Total period of post-treatment observation (days)
5	451711	3 years	Tartar emetic; streptomycin	33	10.0	Failure [1]	0
6	473344	1 year	None	14	4.2	Cure [2]	14
7	101985	4 years	Tartar emetic; fuadin.	20	6.0	Failure	14
8	475740	6 weeks	None	16	5.0	Relapse [4]	38
9	474931	3 years	Tartar emetic	16	4.9	do [4]	41
10	473338	2 years	do	13	4.1	do [4]	58
11	474932	3 months	None	20	6.0	do [4]	35
12	319624	4 years	Tartar emetic	14	4.2	Relapse [3]	44
13	408519	2 years	do	14	4.2	do [3]	39
14	475737	unknown	None	20	6.0	Cure	165

[1] Failure: No obvious response.

[2] Cure: Lesion healed.

[3] Relapse: Partial or complete healing followed by subsequent reappearance of or increase in size of lesion.

[4] Lesions completely healed by 30th day following completion of therapy.

1 has remained cured, and the longest period of observation is 165 days.

Because of the encouraging results at the end of 30 days in the patients listed in table 2, it was decided to give approximately the same amount of drug in a shorter time interval. The one relapse observed in this group was in a patient (case 15) who had had his disease for 21 years. One patient (case 16) showed signs of healing 5 days after discharge. In one patient (case 17) the lesions were healed at the time of discharge from the hospital, but he has not yet returned for further observation. Two patients (cases 18 and 19) have remained well at the end of 41 days.

At this point, due to production difficulties, the supply of oral aureomycin was curtailed temporarily, necessitating further trial with the drug parenterally. A dose of 40 mg. intramuscularly every 8 hours for a total dose of 0.6 gm. in 5 days was used (table 4). Only two patients were treated and one of these (case 21) failed to return to the clinic. The other (case 20) is considered "cured" after a 90-day observation period.

Studies of the effect of aureomycin on the *D. granulomatis* were carried out in the first 19 patients. The organism did not disappear from the lesions during the process of healing, and could still be demonstrated while any ulceration was present. No examinations have yet been made from completely epithelialized lesions.

Table 3.—*Granuloma inguinale treated with 200 mg. of aureomycin orally three times a day*

Case No.	History No. J.H.H.	Duration of disease	Previous treatment	Duration of treatment (days)	Total dose of aureomycin (gm.)	Clinical result	Total period of post-treatment observation (days)
15	200748	21 years	Tartar emetic	10	6	Relapse [1]	17
16	116664	3 months	None	10	6	Healing	5
17	314081	6 weeks	Tartar emetic	10	6	Cure [2]	[3]0
18	478047	3 years	None	10	6	do [2]	41
19	290058	14 years	Tartar emetic	10	6	do [2]	41

[1]Relapse: Partial or complete healing followed by subsequent reappearance of or increase in size of lesion.

[2] Cure: Lesion healed.

[3] No follow-up.

Table 4.—*Granuloma inguinale treated with 40 mg. of aureomycin intramuscularly three times a day*

Case No.	History No. J.H.H.	Duration of disease (months)	Previous treatment	Duration of treatment (days)	Total dose of aureomycin (gm.)	Clinical result	Total period of post-treatment observation (days)
20	421280	3	Tartar emetic	5	0.6	Cure [1]	90
21		7	None	5	.6	Cure?	[2]0

[1] Cure: Lesion healed.

[2] No follow-up.

As aureomycin became more readily available in the form of capsules, and since our experience had already led us to believe that intensive courses might give better and more lasting results, the next 21 patients admitted with a diagnosis of granuloma inguinale were separated into 3 groups (tables 5, 6, and 7).

Patients 22 to 26 inclusive were given 1.0 gm. of aureomycin four times daily for a total of 20 gm. in 5 days.

Patient 22 showed some improvement during the period of administration, but during her stay in the hospital was found to have active pulmonary tuberculosis. The vaginal lesion promptly reverted to its former status, and 30 days after admission to the tuberculosis hospital (60 days after starting aureomycin) a perineal fistula in ano was noted. Although *D. granulomatis* were seen in smears, it is possible that the clinical picture was in part due to or modified by tuberculosis. A course of 20 gm. of streptomycin in 5 days again caused partial healing but the lesion also broke down when the drug was stopped. Guinea pig inoculation

Table 5.—*Granuloma inguinale treated with 1.0 gm. of aureomycin orally four times a day*

Case No.	History No.	Duration of disease	Previous treatment	Duration of treatment (days)	Total dose of aureomycin (gm.)	Clinical result	Total period of post-treatment observation (days)
22	J.H.H. 482312	3 months	None	5	20	Failure [1]	14
23	J.H.H. 490267	3 months	do	5	20	Cure [2]	50
24	J.H.H. 487938	2½ years	Fuadin; tartar emetic	5	20	Relapse [3]	20
25	B.C.H. 125152	12 years	Type unknown	5	20	Cure [2]	0

[1] Failure: No obvious response.

[2] Cure: Lesion healed.

[3] Relapse: Partial or complete healing followed by subsequent reappearance or increase in size of lesion.

from the fistulous tract was done but the report is not yet available. Cultures for *M. tuberculosis* were negative. She is classed as a failure.

One patient (case 23) has remained healed for 40 days, one (case 24) relapsed on the twenty-eighth day following completion of therapy, and one (case 25) has not been seen since discharge although she was healed at that time.

The same total amount of 20 gm. as in table 5 was then administered over a 10-day period to 10 patients (0.5 gm. 4 times daily). Of this group, four (cases 27, 28, 31, and 33) were healed on

Table 6.—*Granuloma inguinale treated with 0.5 gm. of aureomycin orally four times a day*

Case No	History No.	Duration of disease	Previous treatment	Duration of treatment (days)	Total dose of aureomycin (gm.)	Clinical result	Total period of post-treatment observation (days)
26	B.C.H. 124900	2 months	None	10	20	Cure [1]	0
27	B.C.H. 126084	3 months	do	10	20	do [1]	0
28	B.C.H. 126226	6 months	do	10	20	do [1]	36
29	J.H.H. 335387	2 years	do	10	20	Relapse [2]	63
30	J.H.H. 431130	1 month	do	10	20	Cure [1]	0
31	J.H.H. 492858	6 weeks	do	10	20	do [1]	0
32	B.C.H. 125372	2 weeks	do	10	20	do [1]	0
33	J.H.H. 388636	3 to 4 months	do	10	20	do [1]	0
34	J.H.H. 484219	1 year	do	10	20	do [1]	0
35	B.C.H. 126410	1 year	do	10	20	Failure [3]	14
36	B.C.H. 124900	1 year	do	10	20	Cure [1]	0

[1] Cure: Lesion healed.

[2] Relapse: Partial or complete healing followed by subsequent reappearance or increase in size of lesion.

[3] Failure: No obvious response.

discharge but have been lost to further observation. Another (case 34) showed signs of healing but has not been seen since she left the hospital.

One patient (case 29) showed evidence of relapse on the sixty-third day following completion of therapy and another (case 35) failed to show any signs of healing at all. These are both classed as failures.

Only two who have been followed for 30 to 60 days have remained healed.

The last treatment schedule, which is still under study, is one which we hope to prove satisfactory although there are as yet insufficient data from which to make any dogmatic statements.

Table 7.—*Granuloma inguinale treated with 1.0 gm. of aureomycin orally four times a day*

Case No.	History No.	Duration of disease	Previous treatment	Duration of treatment (days)	Total dose of aureomycin (gm.)	Clinical result	Total period of post-treatment observation (days)
37	B.C.H. 126584	1 year	Tartar emetic	10	40	Failure [1]	14
38	B.C.H. 127597	2 years	None	10	40	Cure [2]	0
39	B.C.H. 127124	2 years	do	10	40	do [2]	0
40	B.C.H. 127155	2 to 3 weeks	do	10	40	do [2]	0
41	J.H.H. 491741	3 weeks	do	10	40	do [2]	33
42	B.C.H. 127479	3 weeks	do	10	40	do [2]	0

[1] Failure: No obvious response.
[2] Cure: Lesion healed.

The one failure in this group of patients has also subsequently failed to show any response to a course of streptomycin (40 gm. in 10 days). Although only one patient has been observed for 30 days, all except patient 37 have been healed at the time of discharge from the hospital.

Reactions

Because the toxicity of the drug was not fully known nor the time-dose ratio established, the first 14 patients were watched carefully for untoward reactions. As far as could be determined there were no electrocardiographic changes, disturbances of kidney or liver function, hematologic disturbance, alterations of blood nonprotein-nitrogen or sugar, or allergic reactions. This has been corroborated by at least one other observer (*6*). The hemolytic anemia described during the early trials of the drug was not ob-

served and has subsequently been ascribed to the vehicle used at that time (*2*). Some degree of nausea and diarrhea were noted in almost every patient.

There were, however, severe local reactions to intramuscular aureomycin in all patients at the time of each injection. When the drug was injected into the buttock there ensued severe lancinating pain which radiated down the leg to the knee or ankle. This pain persisted for 15 minutes to 2 hours. Injections in areas other than the buttocks have not been given as yet, at least by the authors.

Discussion

Streptomycin is effective in the treatment of granuloma inguinale, and few untoward reactions have occurred during the short periods of administration required. However, in some cases the organism becomes streptomycin-resistant, necessitating alternative methods of treatment. In such cases, aureomycin may prove to be of value.

We have shown that aureomycin has some effect in healing the lesions of granuloma inguinale, even though (in the dosages we have used) it fails to destroy the organism.

In our experience, parenterally administered aureomycin offers no advantages and the severe local pain precludes this route as a routine measure. The effectiveness of the drug by the oral route permits the hope that it will ultimately be useful in the treatment of patients on an ambulatory basis. It seems to us at least probable that much larger doses, and perhaps longer duration of treatment, than we have so far used may be desirable. We are informed that oral dosages of 3 to 4 gm. daily are well tolerated (*7*). A 250-mg. capsule for oral use is now available. Two new schedules are now being tested: 500 mg. four times a day for 10 days and 1.0 gm. four times a day for 5 days.

Our experience indicates the necessity for an extended post-treatment observation period of at least 60 days before judging the therapeutic efficacy of any antibiotic in granuloma inguinale.

Conclusions

Aureomycin, a new antibiotic, was tested in 42 proved cases of granuloma inguinale.

Aureomycin, when administered intramuscularly in dosages of 20 mg. daily for 23 to 31 days, or 40 mg. three times daily for 5 days, is less effective than streptomycin. In addition, the severe pain accompanying each injection precludes this route of administration as a routine measure.

Aureomycin, when administered orally in total dosages of 4.2 gm. to 40.0 gm. resulted in initially satisfactory clinical responses in 27 of 36 cases. These promising results have stimulated additional studies employing larger amounts of drug. In spite of the effect of the drug in healing the lesions of granuloma inguinale, there is no demonstrable effect on the causative organism.

No untoward effects of aureomycin were observed except local pain.

References

1. WRIGHT, L. T.; SANDERS, M.; LOGAN, M. A.; PRIGOT, A.; HILL, L. M.: Conference on Aureomycin—A New Antibiotic. New York Academy of Sciences, July 21, 1948.
2. WRIGHT, L. T.; SANDERS, M.; LOGAN, M. A.; PRIGOT, A.; HILL, L. M.: The treatment of lymphogranuloma venereum and granuloma inguinale in humans with aureomycin. Ann. New York Acad. Sc., 51: 318, Nov. 30, 1948.
3. GREENBLATT, R. B.; DIENST, R. B.; CHEN, C.; WEST, R.: Oral aureomycin in the therapy of streptomycin-resistant granuloma inguinale. South. M. J., 41: 1121, 1948.
4. GREENBLATT, R. B.: Socioeconomic aspects of granuloma inguinale. J. Ven. Dis. Inform., 28: 181, 1947.
5. KORNBLITH, B. A.: The treatment of lymphogranuloma venereum and granuloma inguinale. New York State J. Med., 46: 1358, 1946.
6. MIRICK, G.: Personal communication.
7. HARDY, S. M.: Personal communication.

The New Threshold in Venereal Disease Control[1]

J. R. Heller, Jr.

In a recent magazine article, William L. Laurence of the New York Times stressed the importance of reducing the lag between scientific discoveries and their application to general use. As an illustration, he told the story of penicillin. The first report of its discovery in 1928 by Fleming of London gathered dust for more than a decade. Then the exigencies of the war years and the great need for such an antibacterial substance brought it forth into the light of scientific development. Sir Alexander said later: "I cannot help thinking of the thousands now dead who would still be alive had interest in penicillin been aroused when I first discovered it in 1928."

It is gratifying to realize that conditions today are far more favorable for prompt recognition and application of scientific

[1] Presidential address before the American Venereal Disease Association, Apr. 8, 1949.

advances—that we are participating in one of the most stimulating eras of medical progression, strengthened and supported by growing public interest and awareness.

Especially in the realm of the venereal diseases has the pace of progress continued strong and steady. We have witnessed a lightning-like series of diagnostic and therapeutic advances for the venereal diseases since the passage of the 1938 Venereal Disease Control Act, which provided sufficient funds to study and act upon every phase of the problem throughout the Nation. With that decisive recognition by Congress and the public, we were very hopeful of great progress. But we could not possibly have foreseen the many startling and heart-warming gains to be made in the brief span of 10 years.

An old friend and co-worker in venereal disease control said to me recently: "I've just been leafing through a 1937 technical journal on the venereal diseases. How sharply it brought back the stubborn problems we had to wrestle with then in the management and treatment of these diseases. It made me feel like a veteran—although that was really not so long ago."

There are many here today who recognize that feeling, the impact of sharp contrast, though their years of service in this field may be no more than 10.

Consider now the public's widespread acceptance and intelligent appraisal of forthright information on the venereal diseases and the problems involved. Public appeal is directed through many channels—by television, radio, films, frequent community demonstrations, newspapers, national magazines; fresh, new ideas for educational projection are continuously being evolved and adapted to areas and population groups; millions upon millions of well-designed pamphlets and posters have been distributed throughout the country in a steady flow.

As a single example of the public response which is now such an integral part of today's picture: a noted radio commentator introduced briefly but concisely on his network program New York City's 1948 VD drive. A flood of 2,000 commendatory letters and requests for pamphlets were received by that health department, not only from each of the 48 States but also from Canada, Hawaii, Panama, and Germany—as a result of that one broadcast. Not one letter was critical. Parents, clergymen, health officers, civic leaders, teachers, and citizens, in their letters, provided the finest kind of direct encouragement and approbation.

Consider also the vigorous studies and demonstrations on case finding which have been widely and continuously carried on for 5 years. These projects have provided an abundance of factual

data for the progressive evaluation of case-finding technics. This evaluation will mean much to the ultimate, full control of venereal disease.

There has been particular emphasis on the value of good contact investigation. This activity, when efficiently done, is a combination of (1) a direct approach to case finding; (2) a personnel-to-patient educational discussion; (3) a cooperative working arrangement between health department and private physician; and (4) good clinical facilities adapted to the areas and population segments to be served. Because the venereal diseases are so closely related to human fallibility and basic human relations, we need to consider carefully all the factors which bring or do not bring infected persons to early examination and treatment.

The facts and figures today present a most encouraging record of steadily declining mortality, of fewer serious complications due to venereal disease, and of a decrease in the early syphilis discovery rate in spite of increased examinations. But it is a record that also puts us on our mettle.

Remembering the American Venereal Disease Association's past record of progressive action, the members of this audience are especially aware that the rich achievements of recent years in the diagnosis, therapy, and epidemiology of the venereal diseases strongly invite continued and concentrated efforts. Only in this way can we strengthen the gains so far made, and move forward with the new concepts which follow one after the other and which promise even richer rewards.

Of the multiplicity of unsolved problems in the biology of syphilis, none is more basic than artificial cultivation of the virulent spirochete. According to Koch's postulates, the specificity of the spirochete in syphilis causation is not fully established until we are able to grow the organism in pure culture. Moreover, research projects will be considerably facilitated when an unlimited source of the pathogenic organism becomes available.

A number of able research workers have attempted and are attempting to cultivate the virulent spirochete. The substance—or substances—present in the living host and essential to survival and growth of the *Treponema pallidum* is unknown to us. Ability to keep the causative organism alive outside the animal body is an essential stepping stone to true understanding of the syphilitic infection. Certain characteristics of the course of this infection—latency, immunity, destruction of the spirochete without resulting cure—suggest a transition form in the organism's life cycle. At any rate, it would seem that this question—among numerous others—will be answered eventually.

We know too that there is a host of variable biologic factors in the blood and tissues of man. Such basic variations may bear a demonstrable relation to the difference in individual responses to syphilitic infection. The variations can be measured. Studied from the point of view of their influence on the invading spirochete, these variable factors should provide a key to the obscure process of immunity.

Differences in the reactions of laboratory animals to infection have been noted by a number of investigators. According to Magnuson, factors which appear to influence the course of acquired immunity include virulence of the organism, size of the inoculum, the duration of the original infection, site and manner of both the original and challenging inoculum, and the degree of local reaction to the first infection. Each of these factors has been studied in experiments with laboratory animals, but investigation of no single factor is yet complete, nor has the relative significance of each in establishing partial or complete immunity been assessed. The whole mechanism of acquired immunity demands continued study.

These remarks are necessarily brief and are intended only as an indication of the broad fields in which the skills of our able investigators are being applied. Only if these essentials of scientific achievement are continuously mobilized and coordinated with the broader public consciousness of human needs can we look forward to true control of venereal disease—in this country and throughout the world.

The Duration of Acquired Immunity in Experimental Syphilis [1]

Harold J. Magnuson, Barbara J. Rosenau, and J. W. Clark, Jr.

This report represents a continuation of our earlier studies attempting to measure quantitatively the degree of acquired immunity in experimental rabbit syphilis. The first report (*1*) dealt with the rate of development and degree of acquired homologous strain immunity during the first 24 weeks after inoculation. It

[1] From the Syphilis Experimental Laboratory, U. S. Public Health Service, University of North Carolina, Chapel Hill, N. C. Aided in part by a research grant of the Research Grants Division, National Institutes of Health, U. S. Public Health Service.

is the purpose of the present paper to describe the degree of established immunity as measured by challenge at varying time intervals after termination of the original 12-week immunizing infection. It will be shown that in rabbits immunized with an original infection of 3 months' duration, there is no change in the degree of acquired immunity during the ensuing 1-year period.

Methods and Materials

In general, the technics employed were identical with those employed in earlier experiments. Male rabbits weighing between 2½ to 3½ kg. at the time of inoculation were inoculated in a single testis with 10^6 *Treponema pallidum* (Nichols strain). Calibration of the inoculums for both original immunizing infection and the challenging inoculation were accomplished in the manner previously described (*2*). The original infection was confirmed by darkfield examination of tissue obtained by testis puncture. Twelve weeks after inoculation, the infection was terminated by the administration of four daily doses of penicillin G in peanut-oil-beeswax to a total of 64,000 units/kg. The challenging inoculation was made 6, 12, 24, or 48 weeks after treatment. These time intervals differ from our earlier experiments in which all challenges were made 6 weeks after treatment. The suitably calibrated challenge inoculation was made into the originally inoculated testis, and the size of challenging inoculums varied between 2×10^2 to 10^7 organisms. Animals were examined twice weekly following reinoculation to detect development of any local lesions. Material from suspicious local lesions was examined by darkfield. The development of a darkfield positive syphiloma at the site of inoculation was considered symptomatic reinfection. In the absence of such symptomatic lesions during the 3-month observation period following inoculation, the animals were sacrificed, both popliteal nodes removed, emulsified and inoculated into the testes of two node transfer animals in the usual manner. These node transfer animals were examined semiweekly for a 3-month period and material from any suspicious testicular lesions was examined by darkfield. If the node transfer animals were positive, the parent animal was considered to have developed an asymptomatic reinfection. The node transfer animals were considered negative only if they remained negative throughout the three month observation period and if the testes removed at the end of this period failed to show *T. pallidum* on darkfield examination. If the original parent was clinically negative and if the node transfer animals were negative, the parent animal was considered immune to the inoculum employed.

In order to determine the relationship of serologic titer to the presence or absence of asymptomatic reinfection, serial bleedings were taken from the central artery of the ear at biweekly intervals following reinoculation. These serums were titered by the VDRL cardiolipin flocculation technic (*3*).

Both the original infecting inoculum and the challenging inoculums were controlled by intracutaneous inoculation of from 2 to 200,000 organisms in the manner previously described (*1*). The adequacy of treatment was controlled by eight animals that were treated, but were not subjected to challenge. Node transfers on these control animals were all negative, including animals subjected to node transfer up to 15 months after treatment.

Results

Shown in table 1 are the results of animals challenged 6, 12, 24, and 48 weeks after treatment. The size of the intratesticular challenging inoculum varied from 2×10^2 to 10^7 organisms. Since none of the animals developed symptomatic reinfection, the symptomatic 50-percent infectious dose, as defined in the previous paper, was greater than the largest challenge employed. The asymptomatic 50-percent infectious dose, which represents that inoculum at which half of the animals may be expected to develop asymptomatic reinfection and the other half remain immune, was

Table 1.—*Degree of acquired homologous strain immunity measured at various time intervals after treatment*

[The original immunizing infection was terminated at 12 weeks after inoculation. Following treatment, intratesticular challenging inoculation was made at the indicated times following treatment with calibrated inoculums as shown. The numbers of animals showing either symptomatic reinfection, asymptomatic reinfection, or immunity are shown in the body.]

Size of inoculum	Time of challenge															
	6 weeks				12 weeks				24 weeks				48 weeks			
	S[1]	A[2]	I[3]	A[1]* I	S[1]	A[2]	I[3]	A* I	S[1]	A[2]	I[3]	A* I	S[1]	A[2]	I[3]	A* I
10^7	0	4	2	20 2												
2×10^6					0	7	3	26 3	0	7	1	15 1	0	3	2	10 2
2×10^5	0	5	2	16 4												
2×10^4	0	6	2	11 6	0	11	0	19 3	0	3	3	8 4	0	4	1	7 3
2×10^3	0	3	2	5 8	0	4	0	8 3	0	4	1	5 5	0	1	2	3 5
2×10^2	0	2	4	2 12	0	4	6	4 9	0	1	6	1 11	0	2	2	2 7
Symptomatic ID_{50}	10^7				2×10^6				2×10^6				2×10^6			
Asymptomatic ID_{50}	5×10^3				6×10^2				2×10^3				5×10^3			

[1] S: Symptomatic reinfection.
[2] A: Asymptomatic reinfection.
[3] I: Immune.
* Reed-Muench.

nearly identical for the four different challenge times. The observed variations are well within the limits of experimental error, since the asymptomatic ID_{50} at 6 weeks was 5×10^3 organisms, at 12 weeks 6×10^2, 24 weeks 2×10^3, and 48 weeks 5×10^3. As in our previous experiments, infections or acquired immunity of considerable duration do not afford end points nearly as sharp as are encountered early in infection. The individual variation among the animals is considerable. On the other hand, the variation is insignificant in comparison with the observed increase in acquired immunity with the increase in duration of the original immunizing infection, wherein the asymptomatic ID_{50} rose from five organisms at 3 weeks to 2×10^5 organisms at 24 weeks.

The present results would indicate that once immunity has been developed it persists for a considerable period of time and in the present experiments exists for at least 1 year without appreciable change in titer. Such immunity would, therefore, appear to be rather permanent.

The results of the serologic tests on these reinoculated animals are summarized in table 2. While such a summary obscures indi-

Table 2.—*VDRL cardiolipin flocculation titers on serums from reinoculated immune animals*

[Animals were immunized by an infection of 12 weeks' duration, terminated by penicillin. The time of the challenging reinoculation varied from 6 to 48 weeks after treatment. Shown are the range of titered STS and their medians arranged by the time and outcome of challenge.]

Time of challenge (weeks)	Result of challenge		At time of reinoculation	Titer					
				Weeks after reinoculation					
				0–2	3–4	5–6	7–8	9–10	11–12
6	A [1]	Median	2	1	3	8	6		8
		Range	1–16	1	1–16	2–16	1–16		1–16
	I [2]	Median	4	2	2	2	2		1
		Range	2–16	½–16	1–16	1–16	½–32		Neg.–16
12	A [1]	Median	1¼	2	1½	1.75	1½	2	1½
		Range	1–4	0–8	0–4	0–8	0–6	0–4	0–4
	I [2]	Median	2	4	2	2	2	2	1
		Range	1–6	1–4	0–4	0–4	½–4	0–4	0–2
24	A [1]	Median	1½	2	2	2	2	2	2
		Range	0–4	0–8	½–6	½–6	0–8	0–4	0–6
	I [2]	Median	1	1	2	1½	1	1	1
		Range	0–4	0–1	0–4	1–6	0–4	0–4	0–4
48	A [1]	Median	1½	1	1	2	1½	2	.75
		Range	1–2	0–4	0–8	0–4	1–4	½–6	0–4
	I [2]	Median		1	1	2	1	2	1
		Range		0–2	½–4	0–2	1–4	0–2	½–2

[1] A: Asymptomatic.

[2] I: Immune.

vidual variations in titer, it may be said that none of the animals, whether asymptomatically reinfected or whether immune, showed any significant rise in serologic titer following reinoculation. This finding is in harmony with our previous finding that animals having had an original immunizing infection of 12 to 24 weeks' duration on reinoculation did not show evidence of increased serologic titer. On the other hand, animals with a short immunizing infection of either 3 or 6 weeks' duration usually showed an increase in serologic titer if reinoculation was followed by symptomatic or asymptomatic reinfection.

Discussion

These experiments are being extended to include longer time intervals between treatment and challenge than our now reported maximum of 48 weeks. The absence of change in immunity during the first year does not necessarily preclude later change. Gastinel and his co-workers (*4*) found that of nine rabbits challenged from 10 to 20 months after treatment, 3 developed symptomatic reinfection compared with 1 out of 20 animals challenged during the first 10 months after treatment. While their data would suggest that there may be a later decrease in immunity, confirmation is necessary.

The approximately thousandfold variation in degree of immunity among animals treated and tested at the same time intervals may be related to the clinical problems encountered in latency and ultimate progression of human syphilis, in which there is also enormous individual variation. It is unknown whether low resistance to homologous strain reinoculation connotes a similar lowered resistance to autogenous spread and progression of the original disease. It is not now possible to measure this experimentally, first, because there is no method which will produce late lesions in experimental animals comparable to those in man, and secondly, because we are dealing with differences in immunity expressed either as complete resistance to inoculation or a partial resistance manifest as asymptomatic reinfection, phenomena which cannot be measured either in man, or in the untreated rabbit. As Chesney (*5*) has emphasized, there have been numerous unsatisfactory attempts to explain the relationship of acquired immunity to ultimate clinical progression and the maintenance of latency. We are little, if any, nearer an adequate explanation of these phenomena than at the time of Chesney's monograph more than 20 years ago.

The obvious need is for a method of determining the degree of

a host's immunity without direct inoculation of the host. Such a method would permit needed studies in man. Perhaps the technics described by Nelson (*6*) for the demonstration of immobilizing antibodies will provide a partial answer to this problem, but our own results to date have not been encouraging in indicating a correlation between the so-called "immobilizing titer" and the degree of immunity as demonstrated by challenge (*7*).

The present experiments suggest that should such a method be available, degrees of immunity detected shortly after treatment may be expected to continue for a considerable period of time. It is possible that such values might have prognostic importance.

Summary

1. In rabbits immunized by a syphilitic infection of twelve weeks duration and terminated by penicillin therapy, quantitative challenge with the homologous (Nichols) strain failed to demonstrate change in immunity measured 6, 12, 24, and 48 weeks after treatment.

2. No symptomatic reinfections were obtained with inoculums as large as 2×10^5 organisms. The asymptomatic 50-percent infectious inoculum was approximately 5×10^3 organisms.

3. No increase in serum reagin titer occurred regardless of whether reinoculation was followed by asymptomatic infection or no infection.

References

1. Magnuson, H. J.; Rosenau, B. J.: The rate of development and degree of acquired immunity in experimental syphilis. Am. J. Syph., Gonor. & Ven. Dis., 32: 418, 1948.
2. Magnuson, H. J.; Eagle, H.; Fleischman, R.: The minimal infectious inoculum of *Spirochaeta pallida* (Nichols strain) and a consideration of its rate of multiplication in vivo. Am. J. Syph., Gonor. & Ven. Dis., 32: 1, 1948.
3. Harris, A.; Rosenberg, A. A.; Riedel, L. M.: Microflocculation test for syphilis using cardiolipin antigen. Preliminary report. J. Ven. Dis. Inform., 27: 169, 1946.
4. Gastinel, P.; Pulvenis, R.; Collart, P.: A propos de l'immunite syphilitique. Du comportement des lapins traites tardivement vis-a-vis de la reinoculation. Compt. rend. Soc. de biol., 128: 739, 1938.
5. Chesney, A. M.: Immunity in Syphilis. Williams and Wilkins, Baltimore, 1927.
6. Nelson, R. A., Jr.; Diesendruck, J. A.; Zheutlin, H. E. C.: Treponemal immobilizing antibodies produced in serum and cerebrospinal fluid during syphilitic infection. (This symposium.)
7. Magnuson, H. J.; Thompson, F. A.: Unpublished data.

Immunological Relationships Between Strains of *Treponema Pallidum*[1]

Thomas B. Turner and Mary C. Cumberland

It is generally recognized that human beings, as a result of infection with *Treponema pallidum,* develop a degree of resistance to second infection. Because of the rarity of second attacks of syphilis it has likewise been concluded that this acquired resistance is probably effective against many different strains of *T. pallidum.*

In the experimental disease most of the studies thus far reported indicate that the immunity developed as a result of syphilitic infection is of a higher order against the homologous strain than against heterologous strains. These latter studies have not been exhaustive, however, and it is really not known whether among strains of *T. pallidum* there are distinct immunological groups as is the case among pneumococci, streptococci, poliomyelitis virus, influenza virus, and many other micro-organisms, or whether this entire species is relatively uniform from an immunological standpoint.

Since this question is one of fundamental importance in a consideration of immunity in syphilis, and may be of great practical importance in the event that it becomes possible to induce immunity by vaccination methods, studies have been undertaken to determine the immunological relationships among representative strains of *T. pallidum.*

Experimental Methods

Source of Strains Tested

Most of the strains of *T. pallidum* listed in tables 1 and 2 are designated by the initials of the patient from whom they were isolated and the year of isolation in rabbits. All such strains were obtained from persons living in Baltimore and presumably infected in that city.

The Nichols strain was isolated in 1912 from the cerebrospinal fluid of a patient with neurorecurrence. The strain has been in rabbits more or less continuously since that time, although several laboratory infections of human beings are known to have occurred, which suggests that the strain has not lost its pathogenicity for man. The strains designated S-4, S-6, and S-10 were isolated

---

[1] From the Department of Bacteriology, the Johns Hopkins School of Hygiene and Public Health, Baltimore, Md.

These studies were supported jointly by grants from the International Health Division of The Rockefeller Foundation, and The Division of Research Grants and Fellowships, National Institutes of Health.

by the senior author in 1933 from persons with early syphilis in Kingston, Jamaica, B.W.I.

Method of Testing Cross Immunity

Two methods of determining the immunologic relationship among strains were employed. In the one, rabbits were infected with a single strain, the Nichols strain, and allowed to develop immunity. Approximately 4 months after the original inoculation they were given a challenge inoculation with one of a number of strains.

The other method was similar except that rabbits were infected originally with one of a number of strains, and approximately 4 months later given a challenge inoculation of a standard dose of the Nichols strain.

Immunizing and Challenge Inoculations

In the first type of experiment, the results of which are shown in table 1, animals were inoculated into both testes with material containing actively motile *T. pallidum* of the Nichols strain. A bilateral syphilitic orchitis commonly developed in 14 to 21 days and some animals subsequently developed generalized lesions of the skin or bones. Active lesions had ordinarily subsided by the ninetieth day after inoculation. It was assumed on the basis of experiments by Chesney and his associates (*1*) and more recently by Magnuson et al. (*2*) that a high degree of immunity to the homologous strain had developed by the end of the fourth month after inoculation.

Table 1.—*Results of challenge inoculation of various strains of* T. pallidum *in rabbits previously infected with the Nichols strain*

Challenge strain	Results of challenge inoculation [1]		Challenge strain	Results of challenge inoculation [1]	
	Nichols immune	Controls		Nichols immune	Controls
LW-38	6/6	4/4	C.J.-39	0/5	4/4
AG-39	0/6	4/4	S4-33	5/5	4/4
MSII-39	0/5	4/4	S6-33	2/5	4/4

[1] Denominator: Number of rabbits challenged. Numerator: Number of rabbits showing lesions.

Between the fourth and fifth months the animals were challenged in groups of four or five with one of the more recently isolated strains. In these experiments frozen material containing large numbers of *T. pallidum* was inoculated intradermally in 0.1-ml. amounts at 4 sites on the rabbit's back. As controls 4 to 8 normal

rabbits were similarly inoculated with the same material. These emulsions which had been preserved at —70° C. had been previously titrated by intradermal inoculation in normal rabbits in order to determine approximately the minimum amount which would regularly produce syphilitic lesions in nonimmune animals.

In the second type of experiment, the results of which are shown in table 2, groups of 4 to 6 rabbits were initially inoculated with one of the strains to be tested. These animals virtually without exception developed typical bilateral orchitis, the experimental disease running a characteristic course. Between 120 and 150 days after inoculation, when the original infection was largely quiescent and the animals were presumed to have a high degree of immunity to the homologous strain, the rabbits were given a challenge inoculation with the Nichols strain. The inoculum in each instance was freshly prepared from an actively progressing syphilitic orchitis and was so diluted that 0.1 ml., which was the amount injected intradermally at each of four sites, contained approximately 500 *T. pallidum.* As controls, 4 to 6 normal rabbits were similarly inoculated with the same material.

In both types of experiments, the test animals were observed for 4 weeks after the control animals first developed syphilitic lesions.

Table 2.—*Results of challenge inoculation of 500* T. pallidum *of the Nichols strain in rabbits previously infected with various strains of* T. pallidum

Immunizing strain	Result of challenge inoculation [1]	Immunizing strain	Result of challenge inoculation [1]
None	22/22	LJW-47	1/6
Nichols	1/15	AH-47	0/5
MSI-39	2/7	FR-47	2/3
MSII-39	0/4	HW-48	1/5
MSS-39	0/3	S-6-33	0/4
LW-38	5/9	S-10-33	0/3
MJ-40	0/4	S-6-33	2/18

[1] Denominator: Number of rabbits challenged. Numerator: Number of rabbits showing lesions.

Standard Strain Challenged by Unknown Strains

In table 1 is presented a summary of the results obtained when rabbits immune to a "standard" strain, the Nichols strain, were challenged with strains whose immunologic relationship to the Nichols strain was unknown. The number of Nichols-immune and normal animals challenged with each strain is indicated by the denominator, and the number of animals developing lesions as the result of challenge inoculation is indicated by the numerator.

It will be noted that all the control animals developed syphilitic lesions, although the incubation period of these lesions varied from strain to strain, as did the size of the individual lesions.

Among the test animals, the Nichols-immune rabbits showed a high degree of immunity to all strains except LW-38 and S-4-33. Examination of the protocols of these experiments shows that even in the case of the latter strains, the lesions developing in the test animals were on the whole considerably smaller than those developing as a result of inoculation of the same material in normal rabbits. Unquestionably, therefore, Nichols animals showed a degree of resistance to these two strains, LW-38 and S-4-33.

Unknown Strains Challenged by a Standard Strain

In table 2 is presented a summary of the results obtained when rabbits infected by, and presumably immune to, one or another of several "unknown" strains were challenged with a standard inoculum, 500 *T. pallidum,* of a "standard" strain.

All the control animals developed large typical syphilomas at the site of inoculation, with a mean incubation period of 21 days. All the so-called unknown strains, except strains LW-38 and FR-47 showed a high degree of immunity to the Nichols strain. Again examination of the protocols of the experiments reveals that even in the case of the latter strains, the lesions developing as a result of the challenge inoculation had a longer incubation period and were substantially smaller than those in the controls, indicating that some degree of cross immunity existed.

Discussion

It is evident that of 14 different strains tested by one or both of 2 methods for cross immunity to the Nichols strain, all but 3 were closely related immunologically to that strain and therefore presumably to each other.

Of those strains which did not clearly show a high degree of cross immunity to the Nichols strain, the data on one—strain FR-47—is clearly inadequate to permit even a tentative conclusion concerning the immunologic relationships involved. The observations on strain S-4 are likewise limited and unfortunately this strain has been inadvertently lost.

It is evident from both tables 1 and 2 that strain LW-38 exhibits less cross immunity to the Nichols strain than do most of the others. Since animals infected with strain LW-38 have not been challenged with the homologous strain it cannot be said whether the evident lack of cross immunity is due simply to the fact that

this strain is a poor antigen, or whether there is a real qualitative difference between this strain and the Nichols strain.

In any case, it would not be justified on the available evidence to conclude that there is more than one immunogenic type of *T. pallidum*, although in the final analysis immunologic groupings among closely related species frequently remain a matter of opinion and convenience. This whole question is receiving further study with the assistance of my associates, Dr. Robert A. Nelson and Dr. Abdul Saleem Khan, using the in vitro test for immobilizing antibodies recently developed by Nelson and Mayer (*3*).

Summary

1. Observations have been made on the immunologic relationship of 14 different strains of *T. pallidum* isolated between 1933 and 1948 to the Nichols strain of that organism, through challenge inoculation of rabbits presumably immune to the strain with which they were originally infected.

2. Eleven of the strains so tested exhibited a high degree of reciprocal immunity with the Nichols strain, which has been perpetuated in laboratory animals since 1912.

3. Of three strains which failed to exhibit such a high degree of cross immunity to the Nichols strain, the data on one were too limited to permit even tentative conclusions concerning the relationships involved. The other two strains seemed to have substantially less cross immunity to the Nichols strain.

4. The data thus far available do not justify the conclusion that there are more than one immunogenic type of *T. pallidum*.

References

1. Chesney, A. M.: Immunity in Syphilis. Williams & Wilkins, Baltimore, 1927.
2. Magnuson, H. J.; Rosenau, B. J.: The rate of development and degree of acquired immunity in experimental syphilis. Am. J. Syph., Gonor. & Ven. Dis., 32: 418, Sept. 1948.
3. Nelson, R. A., Jr.; Mayer, M. M.: Immobilization of *Treponema pallidum* in vitro by antibody produced in syphilitic infection. J. Exper. Med., 89: 369, April 1949.

The Role of Cardiolipin Antigens in the Serology of Syphilis[1]

R. C. Arnold and J. F. Mahoney

Cardiolipin as a new antigenic component now has assumed a major role in the serology of syphilis. In less than a decade the word "cardiolipin" has become almost a generic term meaning—a pure antigenic substance, a pure chemical, an antigen, a test, a type of test, or a diagnostic criterion. The isolation and purification of cardiolipin by Pangborn gave impetus to the development of new antigens, new testing procedures and the modification of existing technics for cardiolipin-type antigens. The syphilologists and serologists have observed the desirable qualities related to sensitivity and specificity of the new type antigen. In the remodeled serologic structure, however, the multiplicity of lipoidal and cardiolipin tests and the noticeable discrepancy of serologic reports in the diagnostic or qualitative range, have created unfavorable and even confusing impressions. At times undue significance may have been placed on the value of incomplete reactions in the weakly-positive or doubtful zone. It is time to delineate the role of cardiolipin in the serology of syphilis and nonspecific diseases.

Cardiolipin is a purified chemical extract of beef heart which, when properly combined with lecithin and cholesterol, forms a serologic antigen. Cardiolipin is not completely new; it is present in varying proportions in all beef heart lipoidal extracts and may influence their sensitivity and specificity as antigenic substances.

The isolation and purification of cardiolipin from beef hearts is a comparatively prolonged and difficult process of chemical extraction. The finished product must pass rigid standards of purity before it may be used. Equally important in the composite antigen is the lecithin component which must be prepared with the same care and must meet equally rigid standards of purity. The third component of the antigen, chemically purified cholesterols, appears to be satisfactory. A complete antigen is compounded by adding the proper proportions of the three components to ethyl alcohol. In addition to the chemical standardization, a serologic assay must be conducted to determine the relationship of the antigenic properties.

A properly prepared cardiolipin antigen is believed to be more specific than the older lipoidal antigens. Moreover, its sensitivity may be adjusted and maintained at a determined level. This level should be established by clinical and serologic studies so that sero-

---

[1] Venereal Disease Research Laboratory, U. S. Marine Hospital, Staten Island 4, New York. Presented at the symposium—Recent Advances in the Study of the Venereal Diseases, 1949.

logic reports will give the clinician the necessary information in treated and untreated syphilis, but will minimize the number of biologic false-positive reactions. The selection of an optimal level of sensitivity for a standard cardiolipin antigen will not be easy because of the many factors involved.

A positive result may be obtained in serum from patients who have untreated syphilis, relapsing syphilis, adequately treated syphilis, and certain diseases, such as malaria, infectious mononucleosis, and others that cause biologically false-positive reactions. Since a positive test does not indicate the active presence of *Treponema pallidum,* the interpretation and evaluation of the positive report must be made by the physician. The positive reaction indicates only that a reactive substance (reagin) of some type is present in the serum. The quantity of reactive substance varies with each individual in health and in disease. A level of sensitivity could be established which would produce a great many or relatively few positive reports, but the extremes would not be suitable for either diagnostic or posttherapeutic studies. A certain level of sensitivity (which may be higher or lower than the present concept) may produce sufficient information in terms of syphilis and yet be relatively free from biologic false-positive reactions.

In considering an antigen for public health use, one must realize that it may be employed in widely separated geographic and climatic areas of this country or even throughout this hemisphere. Hence, it may be necessary to study several different antigen sensitivity levels on serum from both healthy and diseased individuals to secure the necessary data for determining the optimal level of sensitivity. Already one combined clinical and laboratory study is being formulated to survey this problem in untreated and treated syphilis.

A source of confusion in the serology of syphilis is the discrepant picture which occurs when several test procedures are reported. Many tests in common use today employ not only a cruder lipoidal antigen but also an antigen containing cardiolipin and purified lecithin. The results produced by these two antigens, even in the same test, are not always in agreement. Nor do two different tests utilizing cardiolipin-lecithin antigens always react similarly. It is little wonder that the patient, and sometimes the physician, may be bewildered. The obvious solution to this problem is the use of recognized standard procedures.

Under the authority of the Coordinating Committee on Laboratory Methods of the American Public Health Association, a committee has been formed for the purpose of formulating, evaluating, and establishing reference-standard serologic methods for

the serodiagnosis of syphilis. Having once been established, these reference-standard tests could become part of the Diagnostic Procedures and Reagents of the American Public Health Association and could function as do standard methods in the fields of milk and water analysis. The development and adoption of the standard antigens and tests for syphilis by the State Laboratories would not preclude the use of diagnostic procedures that are now employed and may be preferred in the hospital, clinic or private laboratories.

Since the advent of rapidly completed and adequate antisyphilitic therapies (first, intensive arsenotherapy and now, penicillin) more patients with early syphilis are becoming seronegative; also, fewer patients are remaining in the seropositive latent classification, and fewer late manifestations are being observed. With the shrinkage of the reservoir of syphilitic patients, the biologic false-positive potential becomes more important. The number of individuals with biologic false-positive reactions actually may be increasing, or the increase may be only a relative one in relation to syphilitic patients. With further extension of adequate penicillin therapy one may expect the ratio to change even more in the coming decades.

It is therefore increasingly important that only tests of adequate specificity be retained. The increase of specificity-potential contributed by cardiolipin-lecithin antigen to tests for syphilis seems to indicate that this type of antigen is to be recommended until more specific reagents are evolved.

Discussion of the Paper

"The Role of Cardiolipin Antigens in the Serology of Syphilis"

(by R. C. Arnold and J. F. Mahoney)

B. S. Kline [1]

Mr. Chairman, Ladies and Gentlemen:

I was pleased to hear Dr. Arnold say that the cardiolipin antigens had shown themselves to be very valuable in the serodiagnosis of syphilis. As he indicated, these chemically pure antigens are decidedly better for the detection of syphilitic reagin than are the extract antigens. It can be said again, therefore, that Pangborn's

[1] Mt. Sinai Hospital, Cleveland, Ohio.

discovery is the most brilliant contribution to the serodiagnosis of syphilis since the introduction of the Wassermann test.

Our experience now includes work with 13 different lots of cardiolipin and 18 different lots of lecithin. It was found that at a ratio of 6.5 lecithin to 1 cardiolipin, the sensitivity of the antigen was slightly greater than that of the diagnostic Kline antigen emulsion and that at a ratio of about 10 lecithin to 1 cardiolipin, results of maximum sensitivity and maximum specificity were obtained. At ratios of 11 lecithin to 1 cardiolipin, and above, false positive results were obtained with nonsyphilitic sera, increasing with an increasing L:C ratio.

Last year there was reported, from our hospital, a comparison of results of 27,103 slide tests with Kline and optimal cardiolipin lecithin antigens (*1*). In 24,511 tests of nonsyphilitic serums there were 67 false positive reactions with diagnostic Kline antigen emulsion, and only 7 false reactions with optimal cardiolipin lecithin antigen. I doubt if anyone in the room could put a toothbrush into a cup in the bathroom 24,511 times without more than 7 accidents. In addition to this remarkably low false positivity, the slide tests with optimal cardiolipin lecithin antigen gave results somewhat more sensitive with syphilitic serums than those with exclusion Kline antigen emulsion.

Since it was found that the single slide test with optimal cardiolipin lecithin antigen was more specific for the diagnosis of syphilis than with diagnostic Kline antigen emulsion and more sensitive for the exclusion of syphilis than with exclusion Kline antigen emulsion, optimal cardiolipin lecithin antigen was adopted as the standard antigen for our test and Kline antigen used for confirmation.

An example of the value of the superior new antigen in the control of the disease is the record of a case of penicillin treated secondary syphilis.

The slide test with diagnostic Kline antigen emulsion was negative on July 11, 1945. With the exclusion Kline antigen emulsion it was not negative until November 1, 1946. At this time, with optimal cardiolipin lecithin emulsion, it still gave a weakly positive reaction. It was negative with the latter antigen May 22, 1947.

There is a test identical with ours in which the antigen used contains 6.5 parts lecithin in 1 part cardiolipin. In our study this ratio gave results only slightly more sensitive than those with the diagnostic Kline antigen emulsion. It was obvious, therefore, that prompt detection and control of adequate treatment of syphilis could not be achieved by the use of such a low lecithin-cardiolipin ratio, but that this control of the disease was obtainable by the

use of antigens with a ratio of about 10 parts lecithin to 1 part cardiolipin.

Another important matter discussed in this room yesterday and today was the biological false positive reaction. It is our view that most so-called biological false positive reactions are due to adventitious material in the antigen and not to some nonspecific substance in the serum. In the slide test with optimal cardiolipin lecithin antigen (OCLA) and an identical slide test with diagnostic Kline antigen emulsion (DKA), the false positive reactions in 24,511 nonsyphilitic sera were as follows:

Disease or condition	Total tests	OCLA	DKA
Insignificant or no disease	?	1	39
Pregnancy	4,313	0	8
Viral respiratory infection	247	1	8
Jaundice	?	1	3
Abortion	420	0	3
Rectal abscess	41	0	3
Infectious mononucleosis	56	1	2
Seborrheic eczema	2	2	0
Vaccination	?	0	1
Carcinoma	513	1	0
Other	?	0	0
Total	24,511	7	67

These results show that with no adventitious material in the antigen, biological false positive reactions are negligible or nonexistent.

Because results of maximum specificity and maximum sensitivity are obtainable with optimal cardiolipin lecithin antigen, I believe it is here to stay.

Reference

1. Levine, B.; Kline, B. S.; Suessenguth, H.: Clinical and serologic evaluation of 27,103 consecutive slide tests with cardiolipin-lecithin antigen and Kline antigen. Am. J. Clin. Path., 18: 212–217, March 1948.

Delayed Administration of Oral Penicillin as Prophylaxis for Gonorrhea

V. W. H. Campbell, W. J. Dougherty, and C. E. Curtis[1]

The present methods of prophylaxis for venereal disease are not completely effective. Early use is mandatory, but delayed use occurs because facilities and materials are frequently not available. Improper application results are due to incomplete knowledge, or to the condition of the subject. Finally, in practice present methods have not been utilized by large numbers of individuals. The use of oral penicillin for prophylaxis of venereal disease, if effective, would provide a simple method of prophylaxis which would eliminate many objections. The early use of oral penicillin prophylaxis has been reported (*1*) as highly effective in the prevention of gonorrhea. The effectiveness of oral penicillin prophylaxis following delayed administration had not been evaluated previously.

The operation of a Naval Force in an area where high venereal disease rates prevailed afforded the opportunity to conduct a study designed to determine the feasibility and efficiency of prophylaxis by oral penicillin given 12 to 24 hours after exposure to venereal infection.

Method

Two important factors are present in this study: (1) participation by the men was entirely voluntary; (2) the uncertain efficiency of the oral prophylaxis and the use of placebos prevented the use of penicillin prophylaxis as the sole method, and dictated the recommendation of standard Navy prophylactic procedures.

It is recognized that a far more effective study would have resulted had no adjuvant prophylactic measures been used.

Throughout the cruise it was urged that men who were exposed sexually while on liberty report to prophylactic stations following exposure. Men were informed that this was the first condition of voluntary participation in the study.

The Naval Force spent 14 days at sea prior to entering the area. This provided ample time to discover all cases of gonorrhea incident to the last port of call.

[1] Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy.

Table 1.—*Time interval in days at sea and in port, June 6 to July 26*

	At sea	I		II		III	
		Port	At sea	Port	At sea	Port	At sea
Days	14	5	4	6	1	5	14

Alternate periods were spent at sea and in port as shown in the above table.

While in port men were granted liberty on alternate days. These factors provided reasonable assurance of assigning gonorrheal infection to a specific period of exposure.

Volunteer participants were divided into experimental and control groups by odd and even serial numbers. A placebo was administered to the control population and 200,000 units of oral sodium penicillin G was given to the experimental group at 8:00 a.m. on the morning following liberty. This provided a minimum elapsed interval from exposure to oral penicillin prophylaxis of approximately 8 hours. This time was chosen because it is generally applicable to liberty experience throughout the Navy. The identity of the tablets remained secret throughout the study.

Once an individual participated in the study, his records were continued in each instance of recorded exposure whether or not he utilized station prophylaxis or the experimental agent. The records maintained for each man contained: name, serial number, date, time of exposure, number of exposures, time of standard prophylaxis, and time of taking oral tablets for each recorded exposure. Due to the voluntary character of this study, records of incomplete participation occurred. This human factor will complicate any prophylactic study, and it was minimized in the present study by including only those records of complete participation.

Each man was entered in the study only if evidence existed that he received both a station prophylaxis and an oral tablet following each liberty in which recorded exposure occurred. In the control group, only those men were included who received station prophylaxis on every liberty for which exposure was recorded. Strict adherence to the use of the placebo was not required. All records not fulfilling the above criteria were discarded.

In cases of multiple exposure on a single liberty, the time of exposure was not designated for each exposure. Exposures averaged 1.4 per liberty and varied from 1 to 11 per liberty, with no record of the number of partners involved. To simplify the sta-

tistical analysis the time intervals are considered to be the interval elapsing from the last exposure, to station prophylaxis, and to the oral tablet. This imposes bias, in cases of multiple exposure only, against the effectiveness of both the chemical and the penicillin prophylaxis because the time is being measured in terms of a minimal interval, whereas the interval may be maximum.

The definition of the most probable period of infectious exposure was accomplished by the ship's medical officer as a result of a detailed history taken at the time of appearance of symptoms. Diagnosis was established by physical findings and by microscopic examination of the urethral exudate. Cultural methods were not available.

Results

Of the approximately 3,000 men who participated in the study, the records of 2,080 men were retained because they fulfilled the requirements established in the criteria.

There were 1,059 men in the experimental group and 1,021 in the control group. Table 2 indicated the number of liberties, exposures, and cases of gonorrhea directly attributed to these liberties and exposures. The number of exposures reported are not quite the true total, as one ship routinely recorded 1 exposure per liberty. Although the number of cases of gonorrheal infection is small, nevertheless, table 2 indicates a 58-percent reduction in rate in the penicillin group as compared with the placebo group.

Table 2.—*Gonorrhea—penicillin and control group rates, Naval Forces, July and August 1948*

Group	Number of men	Number of cases of gonorrhea	Number of liberties	Rate per 1,000 liberties	Number of exposures	Rate per 1,000 exposures
Penicillin	1,059	9	1,833	4.9	2,625	3.4
Control	1,021	22	1,891	11.6	2,686	8.2

Exposure was followed within an hour by standard prophylaxis in both the experimental and control groups in approximately 63 percent of all man liberties. The distributions, both control and experimental shown in table 3, appear to be comparable within the limits of chance variation. Contrary to anticipation, a high proportion of infected cases, both control and experimental, received prophylaxis within one hour of exposure.

The mean elapsed interval from exposure to ingestion of penicillin is observed to be 15 hours. The records of the infected cases in the penicillin group indicate that the least elapsed interval be-

Table 3.—*Distribution of man liberties by time interval between exposure and station prophylaxis*

Time	Man liberties					
	Experimental group			Control group		
	Number	Percent	Cases	Number	Percent	Cases
Total	1,833	100	9	1,891	100	22
Less than 1 hour	1,140	62	7	1,209	64	14
1 to 2 hours	231	13	0	243	13	3
2 to 5 hours	280	15	1	241	13	2
5 hours and over	181	10	1	198	10	3

tween exposure and the taking of penicillin tablets, is 10 hours. Table 4 indicates the distribution of man liberties in terms of the time interval between exposure and utilization of oral penicillin tablets.

Table 4.—*Percentage distribution of man liberties by time interval*[1] *between exposure and administration of oral penicillin prophylaxis*

Time	Man liberties		Cases of gonorrhea
	Number	Percent	
Total	1,833	100	9
Less than 8 hours	7	0	0
8 to 12 hours	453	25	3
12 to 16 hours	709	39	2
16 to 20 hours	499	27	4
20 hours and over	165	9	0

[1] Mean interval 15.0 hours. Standard deviation 4.0 hours.

The prophylactic effectiveness of oral penicillin in the prevention of syphilis, and the possibility of this procedure masking syphilis were considered. A Kahn survey conducted subsequent to the cruise revealed two individuals in the control group and three in the experimental group to have positive serologic tests for syphilis. None of these men are recorded as having darkfield positive lesions. Two men were recorded as having negative serologic tests for syphilis in March 1948 and three had no previous serologic tests for syphilis. It was impossible to assign the probable date of these five infections. Consequently no conclusion can be drawn as to the effectiveness of oral penicillin prophylaxis in the prevention of syphilis or to the possibility of masking syphilis.

Reactions to penicillin were not observed during this study although all medical officers were constantly on the alert for such reactions.

Because it was felt that conditions of storage, temperature, and humidity at sea might affect the potency of the drug, two series of blood level determinations were conducted on the oral penicillin utilized in this experiment. The initial series was run simultaneously with the experiment at sea, and the second series immediately after return to continental United States. Figure 1 indicates the comparability of levels and the continued effectiveness of the tablets. After the experiment, the tablets were also assayed by the Food and Drug Administration, in Washington, D. C., and found to conform to the original assay.

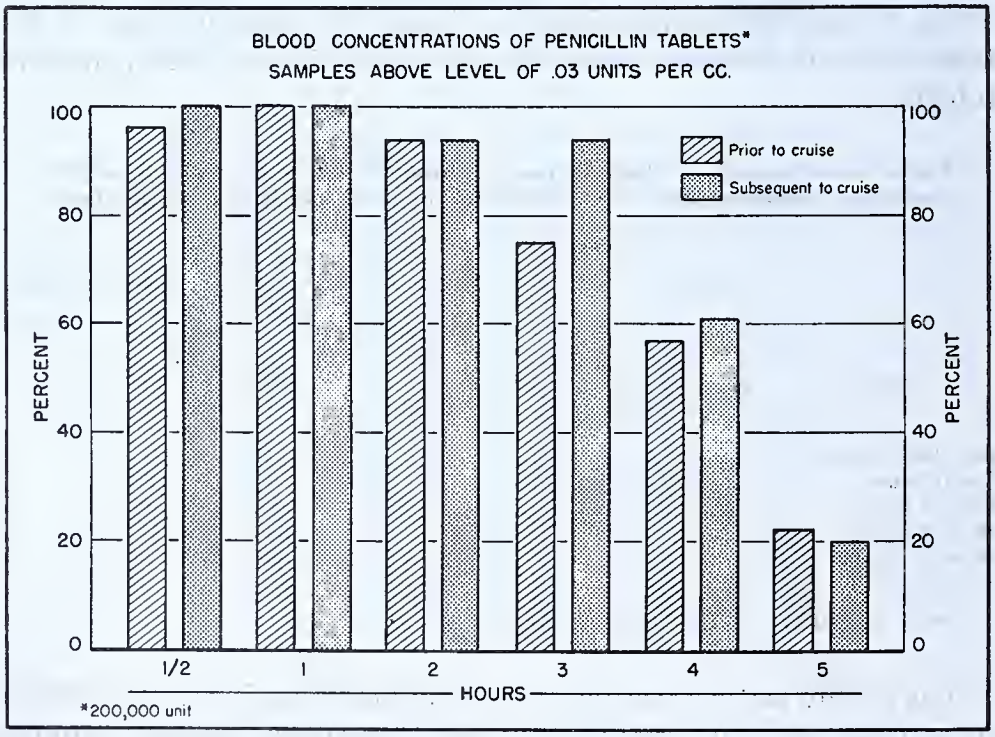


FIGURE 1.

Discussion

The incidence of gonorrhea in the control group is 11.6 per 1,000 liberties, and in the group receiving 200,000 units of oral penicillin is 4.7 per 1,000 liberties. These rates are based upon liberties in which exposure was known to have occurred. In the initial study of oral penicillin prophylaxis (*1*), the incidence of gonorrhea per 1,000 liberties was 11.9 per 1,000 for the control group, and less than 1 per 1,000 for the group which received 250,000 units of

penicillin. These rates were based upon the administration of penicillin following all liberties regardless of exposure on the debatable assumption that liberty and exposure were synonymous. In the earlier study the probable average elapsed time between exposure and oral penicillin was 2 hours. In contrast, the average minimal elapsed time between exposure and utilization of oral penicillin is 15 hours in the present study. It is obvious that strict comparison of the two studies is not justified.

The results of this experiment tend to strengthen the evidence that oral penicillin is effective as a prophylactic agent in the control of gonorrhea. It further indicates that with an increasing interval of time between exposure and utilization of penicillin tablets the efficiency is reduced. This is to be expected because in experimental infections with other diseases, the longer the incubation period, the larger the dose of penicillin required for cure. In view of the failures in the penicillin group of this study using 200,000 units of penicillin orally at an interval of 15 hours after exposure it appears that the dosage should be increased or that the time interval from sexual exposure to ingestion of penicillin should be decreased to obtain more effective results.

The effect of standard prophylaxis exerted in this experiment is believed to be the same in both experimental and control groups. This is based upon the assumption that the utilization of such prophylaxis is demonstrated to be comparable in terms of time from exposure. Therefore it may be assumed that the results observed are indicative of the action of oral penicillin. No evaluation of the variable efficiency of standard prophylaxis as used in this study is possible. It is, however, believed that the random-sampling method and the size of the groups attained in this study resulted in two groups which may be considered reasonably identical within the criteria established.

Numerous difficulties were anticipated and encountered in attempting to obtain precision in this type study which deals so intimately with the problem of human sexual relations. Many variable factors are present to confuse the results. For example, how infectious are the exposures that are utilized as a denominator? The exposures of a brothel are probably more comparable than disseminated exposures to a variety of promiscuous pick-ups. What is the effect of multiplicity of exposures and partners? What effect has the duration of intercourse on the required concentration of the infective agent? What is the effect of various prophylactic measures such as soap and water hygiene, the condom, and chemical prophylaxis, singly or in combination? What is the experience of any one individual over a series of exposures?

How well will the men cooperate, in use of the agent, in recording exposure, and other factors?

The preceding variables are emphasized because the implications attendant upon the acceptance of oral penicillin as a general prophylactic measure are sufficiently grave to warrant precise analysis of its effectiveness.

Several questions of public health significance are yet to be answered. First, the question as to whether daily, or near daily, use of oral penicillin in prophylactic doses, or in higher doses, will suppress the primary and secondary lesions of syphilis. In gonorrhea acquired due to delayed utilization of oral penicillin prophylaxis, will the daily, or near daily use of oral doses suppress the disease to a subclinical stage? This suppression may permit an infected individual to expose to risk a variety of partners resulting in further transmission of disease and increasing the public health problem of gonorrhea and syphilis.

Since public awareness of the efficiency of penicillin in the therapy of gonorrhea may result in widespread self-medication and the attendant dangers of inadequate therapy if oral penicillin tablets are made available to the laity, cautious acceptance is urged of the result of any experiment in this field.

In the routine therapy of gonorrhea, cases are rarely observed which fail to respond to 300,000 units to 1 million units of penicillin parenterally. In these dosages, the gonococcus is killed. However, due to the fact that the blood levels achieved by oral tablets in prophylactic dosages are much lower than those achieved by routine treatment, it seems probable that selective survival of the gonococcus may occur since this has been demonstrated with other organisms (*2*). Such selection may permit propagation of more resistant organisms which in the presence of continued minimal concentrations of penicillin might adapt and increase in resistance. Although laboratory evidence seems to indicate that this will occur less readily than it did with sulfa drugs, nevertheless, it is believed to present a potential public health hazard of such extreme importance as to require the most thoughtful consideration.

These factors, along with the possibility of occasional sensitivity reactions, demand that this form of therapy continue to remain under the supervision of the medical profession.

Conclusions

1. Two hundred thousand units of oral penicillin utilized on the average of 15 hours after exposure reduced by over one-half the gonorrheal attack rate in a selected group of naval personnel.

2. It is recommended that the dosage of penicillin be increased or that the time interval from sexual exposure to oral administration be decreased in future studies.

3. The evaluation of the effectiveness of oral penicillin in the prophylaxis of gonorrhea is dependent upon precise measurement of a large number of variables which in a voluntary study is most difficult.

4. The public health hazards, suggestions for future studies, and unanswered problems are discussed.

5. The true value of penicillin in the prophylaxis of venereal disease will be more readily demonstrated when it is utilized as the sole agent.

6. Further experimentation on this method is necessary and desirable.

Acknowledgment

The oral penicillin tablets and placebos used in this study were supplied through the courtesy of the Commercial Solvents Corporation.

Acknowledgment is extended to Dr. Harold Hirsh, Georgetown University Laboratory, Gallinger Municipal Hospital, Washington, D. C., for determining the penicillin blood level concentrations recorded in this study.

References

1. Eagle, H.; Gude, A. V.; et al: Prevention of gonorrhea with penicillin tablets. Pub. Health Rep., 63: 1411–1415, Oct. 29, 1948.
2. Tillet, W. S.: The antibiotic age. Am. J. Med., 4: 159, Feb. 1948.

Revised Criteria of Cure in Gonorrhea [1]

Adolph Jacoby and Theodore Rosenthal

With the introduction of newer and more effective therapeutic measures in gonorrhea, the time required for completion of the tests of cure has been steadily shortened. Before the sulfonamide era, our criteria of cure covered a minimum period of 3 months.

[1] Read at the meeting of the Syphilis Study Section and the American Venereal Disease Association on April 7, 1949, at Washington, D. C.

From the Bureau of Social Hygiene, Department of Health, City of New York. Acknowledgment is made to the Statistical and Tabulating Division of the Health Department for the collection and tabulation of this material.

This time has been reduced so that at present the time for completion of posttreatment observation is 3 weeks. The criteria of cure now in use is as follows:

For males—Disappearance of clinical signs and symptoms, followed by three negative urethral and prostatic smears and cultures taken at weekly intervals.

For females—Disappearance of signs and symptoms, followed by three negative urethral and cervical smears and cultures taken at weekly intervals.

To determine whether it is practical and safe from the medical and public health standpoints to reduce this period of observation the following study was undertaken.

Gonorrhea cases admitted during a single month (October 1948) were included in this study. A total of 1,131 patients treated for gonorrhea by a single intramuscular injection of 300,000 units of penicillin in oil and beeswax was surveyed. There were 885 males and 246 females in this group. Of the males, 234, and of the females, 32, failed to return for any posttreatment examination. The remaining 651 males and 214 females had at least one posttreatment smear and culture. Four hundred one males and 158 females returned for a second posttreatment smear and culture. Two hundred fifty-nine males and 105 females returned for a third smear and culture.

Table 1.—*Posttreatment observations and examinations*

	Males		Females	
	Number	Percent	Number	Percent
Total cases	885	100.0	246	100.0
No examination	234	26.4	32	13.0
Returned for:				
At least 1 posttreatment observation	651	73.6	214	87.0
At least 2 posttreatment observations	401	45.3	158	64.2
At least 3 posttreatment observations	259	29.3	105	42.7

Of the 214 females who returned for posttreatment observation, positive smears or cultures were found among 30, a total failure rate of 14 percent. Eighteen positive smears and cultures were found on the first examination or a failure rate of 8.4 percent; of the 158 reporting for a second smear and culture, 6 were positive, and of the 105 reporting for a third smear and culture, an additional 6 were positive, making an additional failure rate on second and third cultures of 5.6 percent.

Table 2.—*Result of posttreatment examination of females*

	Number of examinations	Number of positive cultures and smears	Cumulative percent positive
Total	214	30	14.0
First examination	214	18	8.4
Second examination	158	6	11.2
Third examination	105	6	14.0

Of the 651 males who returned for posttreatment observation, a total of 78 were found positive on smear and culture, a failure rate of 12 percent. Forty positive smears or cultures were found on the first examination, a failure rate of 6.1 percent. Of the 401 having a second smear and culture, 24 were positive, and of the 259 reporting for a third smear and culture, 14 were positive making an additional failure rate of 5.9 percent.

Further study of these 38 positive smears and cultures on second and third examinations shows that 14 were positive at examinations made later than 21 days after treatment, and of the remaining 24, 10 were positive on smear examinations only. It is justifiable to consider these 24 patients (14 positive after 21 days, and 10 with positive smears) as in all probability reinfections rather than treatment failures. In any case, these presumable reinfections would have returned voluntarily for re-treatment because of reappearance of symptoms. Eliminating these 24 positives would reduce the 5.9 percent of additional failures on second and third examination to 2.2 percent.

Table 3.—*Result of examination of males*

	Number of examinations	Number of positive cultures and smears	Cumulative percent positive
Total	651	78	12.0
First examination	651	40	6.1
Second examination	401	24	9.8
Third examination	259	14	12.0

Discussion and Summary

In all patients admitted for acute gonorrheal infection in New York City Health Department clinics during October 1948, 73.6 percent of men and 87 percent of women returned within one week for a posttherapy smear and culture; only 29.3 percent of men and

42.7 percent of women presented themselves for three consecutive examinations. An additional total of 2.2 percent of failures among males would have been detected by such second and third culture examinations.

In the females, even assuming that all positive results obtained on second and third examinations were failures, a maximum of 5.6 percent would have been detected in addition to the failures found on the first examination.

With only one-third to one-half of patients returning at weekly intervals for three cultures and a possible failure to detect an additional 2.2 percent to 5.6 percent of patients not responding to therapy by elimination of the second and third examinations, it would appear that the loss by omitting such second and third examinations can reasonably be assumed without serious detriment to control efforts in this disease. Furthermore, the time and personnel required in case holding of this type can be utilized more profitably in other phases of the venereal disease control program.

Conclusion

In view of the above findings, it is proposed to limit examinations in New York City Health Department clinics, for the determination of cure, to a single posttreatment smear and culture made within 7 days after treatment is administered, and to discharge patients who are negative on these examinations.

Reports of the North Carolina Syphilis Studies [1]

II. An Evaluation of Case-Finding Measures in Multiple Episodes of Infectious Syphilis [2]

John J. Wright and Cecil G. Sheps

Introduction

In a previous article (*1*), the authors discussed the importance of careful evaluation of the effectiveness of various case-finding measures in newly discovered cases of syphilis. This report is of a similar analysis of 142 cases of infectious syphilis, due either to relapse or to reinfection, with lesions visible to the patient, which occurred in patients who had received previous treatment for syphilis. Inasmuch as all the patients involved in this series had been given previous treatment, they all had received a measure of directed venereal disease education. It might, therefore, be expected that such individuals would present a different type of problem so far as the relative effectiveness of various case-finding procedures was concerned.

Method of Study

The North Carolina Syphilis Studies and their field of operation have been described in a previous article (*1*). The data presented here include all Negro cases registered with the Venereal Disease Clinic of the Durham City and County Health Department during 1944 through 1947. The patients selected met the following criteria:

1. Each had a history of at least one previous diagnosis of syphilis and treatment.
2. Each had a current diagnosis of primary or secondary syphilis, either reinfection or infectious relapse.
3. Each had one or more lesions visible to the patient at the time of diagnosis. Cases of serorelapse without lesions and cases in which the lesions were not visible to the patient, such as intravaginal lesions, were not included. For the purposes of this study, no attempt is made to differentiate between relapse and reinfection. The data used were secured from the clinical record and

---

[1] From the School of Public Health, University of North Carolina. These studies are supported jointly by grants from the International Health Division of the Rockefeller Foundation and the North Carolina State Board of Health.

[2] Presented at the Eleventh Annual Session of the American Venereal Disease Association, Washington, D. C., April 8, 1949.

ACKNOWLEDGMENT: The authors wish to express appreciation to the Superintendent of the Durham City and County Health Department and to the Director and staff of its Venereal Disease Clinic, whose cooperation made this study possible.

from the special epidemiologic record form designed for research purposes and completed at the time of interview. It is believed that each case was assigned to the correct "reason for admission," because special attention was paid to this matter as part of the research being conducted by this group. This analysis was restricted to Negro cases because there were insufficient cases among white persons to justify studying the latter.

Classification of Case-Finding Methods

The classification of case-finding methods is a functional one in terms of what brought the patient to recognition, regardless of the referral agency; it falls into three groups, each requiring quite different activities on the part of the health department.

1. Administrative and field methods requiring special effort directed toward selected individuals.

(*a*) Investigation of sexual, family, and suspected contacts.

(*b*) Follow-up of previously treated syphilitic patients who lapsed from treatment and routine follow-up, did not respond to a reminder post card, and required vigorous additional effort (a field visit or the use of legal measures) to bring them back to the clinic.

2. Educational methods directed toward either selected or unselected groups, resulting in voluntary application for diagnosis on the patient's initiative.

3. All other methods:

(*a*) Routine follow-up examination of persons previously treated, resulting in discovery of new cases through noting a rise in serologic titer, which led to further examination, or through the discovery of lesions which had escaped the patient's notice.

(*b*) Examination of persons suspected, due to circumstantial evidence, of having syphilis (jail inmates, "beer joint" habitues, etc.).

(*c*) Examination of military personnel whose disease was discovered by routine examination in the armed services at the time of induction into or separation from the service and who were then referred to the health department.

(*d*) Examinations required by law (premarital, prenatal, and for health certificates required by food handlers, domestic servants, beauticians, and barbers).

Analysis of Data

The data were classified and tabulated by case-finding method according to the following characteristics:

1. Sex.
2. Time lapse since last treatment.
3. Duration of lesion.
4. Agency of previous treatment.
5. Comparison of case-finding methods at time of previous and present diagnoses.

In the tables which present the data, the percentages do not add up to precisely 100 percent in some instances; these differences in summation are due to rounding. The Chi square goodness of fit was used to test the statistical significance of the data.[3]

Results of Study

A total of 142 cases of syphilis which met the criteria established for this study were observed among 127 individuals. Among males, 63 cases were seen in 57 individuals, of whom 6 had two separate episodes of syphilis in the period studied. Among females, 79 cases were found in 70 individuals, of whom 7 had two separate episodes of syphilis and 1 had 3 during the period studied.

There were 50 additional cases of infectious syphilis, reinfection, or relapse that were omitted either because there were no lesions visible to the patient or because reliable information regarding the case-finding procedure was not available.

Summary of Case-Finding Methods

As shown in table 1, out of the total of 142 cases, contact investigation brought 41 cases to diagnosis, and the follow-up of lapsed patients located 22; thus, administrative and field methods requiring special effort brought 63 cases (44.4 percent) to diagnosis. Educational methods resulting in finding the case through the patient's initiative brought 59 cases (41.5 percent) to diagnosis. All other methods were responsible for locating only 20 cases (14.1 percent).

Analysis of Case-Finding Methods by Sex

Table 1 and figure 1 show the case-finding methods by sex. Out of the whole group of 63 male cases, the contact-tracing procedure brought 14 to diagnosis, and the vigorous follow-up of lapsed patients located 10; thus, administrative and field efforts directed toward selected individuals brought 24 cases (38.1 percent) to recognition. Educational methods resulting in the patient seeking treatment were responsible for finding 36 cases (57.1 percent). All other methods brought 3 cases (4.8 percent) to diagnosis.

[3] Grateful acknowledgment is made to the Institute of Statistics, Greater University of North Carolina, for assistance in this phase of the analysis.

Table 1.—*Number and percentage of cases* [1] *by sex and case-finding method*

Case-finding method	Total		Male		Female	
	Number	Percent	Number	Percent	Number	Percent
Methods involving special effort:						
Contact investigation	41	28.9	14	22.2	27	34.2
Vigorous follow-up of lapsed cases	22	15.5	10	15.9	12	15.2
Patient's initiative	59	41.5	36	57.1	23	29.1
All other methods	20	14.1	3	4.8	17	21.5
Total	142	100	63	100	79	100

[1] Negro cases with previous history of diagnosis and treatment of syphilis, current diagnosis of primary or secondary syphilis (reinfection or infectious relapse), and lesion visible to patient.

The female cases present a somewhat different picture. Out of the entire group of 79 cases, contact investigation brought 27 cases to the clinic and the follow-up of lapsed cases brought 12, a total of 39 cases (49.4 percent). The patient's initiative brought 23 cases (29.1 percent) to attention. All other methods were responsible for locating 17 cases (21.5 percent): the primary factor involved in this group was routine screening examination to satisfy legal requirements (food handlers, premarital, and prenatal).

Special attention is drawn to the difference between males and females in the relative effectiveness of the major case-finding measures. Administrative and field efforts directed toward selected individuals were responsible for bringing to attention virtually half of the female cases and almost two-fifths of the male

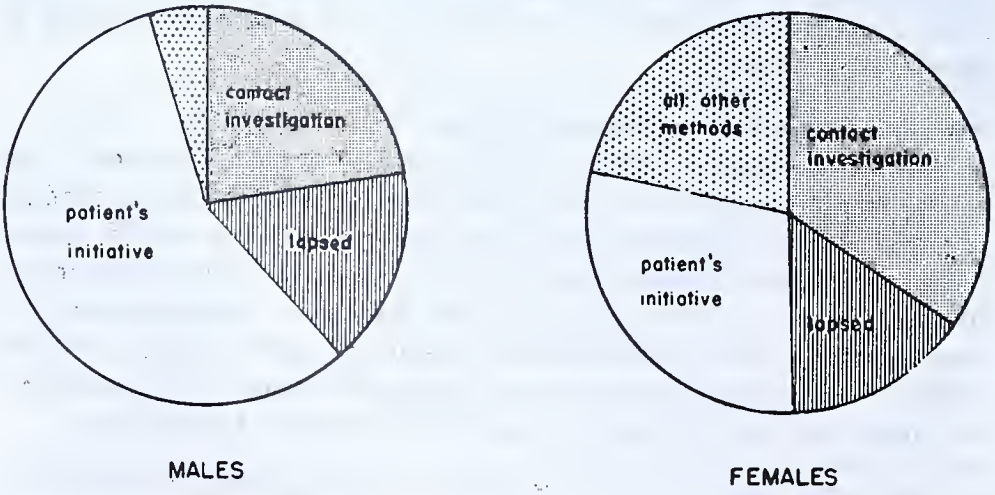


FIGURE 1.—Case-finding methods in infectious syphilis by sex—Negro. (Reinfection or relapse.)

cases. Whereas over half the male cases came to diagnosis through the patient's initiative, the proportion of females in this classification was much smaller, being roughly 30 percent.

The distribution of case-finding methods described in this section was significantly different from that which would have occurred by chance alone.

Analysis of Case-Finding Methods by Time Interval Since Last Treatment

Table 2 presents the data, by sex, according to the length of time since the last treatment was received for syphilis prior to the present episode. The cases were classified into four groups based on the date of the last treatment prior to the present episode: (1) less than 1 year, (2) 1 year or more but less than 2 years, (3) 2 years or more, and (4) unknown.

The available data do not appear to follow any decisive pattern, and the distribution of case-finding methods was not found to be statistically significant.

Analysis of Case-Finding Methods by Duration of Lesions

Table 3 presents the data, by sex, according to the duration of the visible syphilitic lesions before diagnosis. The cases were classified into four groups: (1) syphilitic lesions visible less than 2 weeks, (2) from 2 through 3 weeks, (3) 4 weeks or more, and (4) unknown.

Again there is no clearly discernible pattern and the distribution of case-finding methods was not significant statistically.

Analysis of Case-Finding Methods by Agency of Previous Treatment

Table 4 presents the data, by sex, according to the agency of former treatment (rapid treatment center, armed services, public health clinic, private physician, and other). There is no clearly demonstrated pattern, and the distribution of case-finding methods was not significant statistically.

Comparison of Case-Finding Methods at Time of Previous and Present Diagnosis

Reliable information was available regarding the case-finding mechanism involved in bringing the case to recognition at the time of the previous diagnosis in 88 out of the 142 cases considered in this study. These data, presented in table 5, represent 36 male and 52 female cases; because of the essential similarity of the data for both sexes, they are presented in a combined table. The number of cases which came to diagnosis through the patient's initiative decreased from 32 at the time of the previous diagnosis to

Table 2.—*Time lapse since last treatment of previous episodes,*[1] *by sex and case-finding method*

[Number and percentage]

Case-finding method	Time lapse since last treatment of previous case															
	Less than 1 year				1 to 2 years				2 years or more				Unknown			
	Male		Female		Male		Female		Male		Female		Male		Female	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Methods involving special effort:																
Contact investigation	8	20.0	7	18.4	5	41.7	12	54.5	1	11.1	7	41.2	0	0	1	50
Vigorous follow-up of lapsed cases	8	20.0	9	23.7	2	16.7	3	13.6	0	0	0	0	0	0	0	0
Patient's initiative	22	55.0	13	34.2	4	33.3	4	18.2	8	88.9	5	29.4	2	100	1	50
All other methods	2	5.0	9	23.7	1	8.3	3	13.6	0	0	5	29.4	0	0	0	0
Total	40	100	38	100	12	100	22	100	9	100	17	100	2	100	2	100

[1] Negro cases with history of previous diagnosis and treatment of syphilis, current diagnosis of primary or secondary syphilis (reinfection or infectious relapse) and lesion visible to patient.

Table 3.—*Length of time lesion was visible to patient before diagnosis,*[1] *by sex and case-finding method*

[Number and percentage]

Case-finding method	Length of time lesion was visible to patient before diagnosis															
	Less than 2 weeks				2 through 3 weeks				4 weeks or more				Unknown			
	Male		Female		Male		Female		Male		Female		Male		Female	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Methods involving special effort:																
Contact investigation	4	15.4	8	40	3	20.0	3	17.6	4	33.3	11	47.8	3	30	5	26.3
Vigorous follow-up of lapsed cases	6	23.1	4	20	3	20.0	3	17.6	0	0	1	4.3	1	10	4	21.0
Patient's initiative	16	61.5	7	35	8	53.3	8	47.0	8	66.6	5	21.7	4	40	3	15.8
All other methods	0	0	1	5	1	6.7	3	17.6	0	0	6	26.1	2	20	7	36.8
Total	26	100	20	100	15	100	17	100	12	100	23	100	10	100	19	100

[1] Negro cases with history of previous diagnosis and treatment of syphilis, current diagnosis of primary or secondary syphilis (reinfection or infectious relapse), and lesion visible to patient.

Table 4.—*Agency which treated previous episode,[1] by sex and case-finding method*

[Number and percentage]

Case-finding method	Agency which treated previous case															
	Rapid treatment center				Armed services				Health department clinic				Private physician and other			
	Male		Femal		Male		Female		Male		Female		Male		Female	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Methods involving special effort:																
Contact investigation	7	21.9	18	37.5	4	28.6	0	0	1	8.3	8	32.0	2	40.0	1	16.7
Vigorous follow-up of lapsed cases	9	28.1	12	25.0	0	0	0	0	1	8.3	0	0	0	0	0	0
Patient's initiative	15	46.9	10	20.8	9	64.3	0	0	9	75.0	11	44.0	3	60.0	2	33.3
All other methods	1	3.1	8	16.7	1	7.1	0	0	1	8.3	6	24.0	0	0	3	50.0
Total	32	100	48	100	14	100	0	0	12	100	25	100	5	100	6	100

[1] Negro cases with history of previous diagnosis and treatment of syphilis, current diagnosis of primary or secondary syphilis (reinfection or infectious relapse), and lesion visible to patient.

Table 5.—*Comparison of case-finding methods at time of previous and present diagnoses* [1]

[Number and percentage]

At time of previous diagnosis			At time of present diagnosis							
Case-finding method	Number	Percent	Contact investigation		Vigorous follow-up of lapsed cases		Patient's initiative		Other	
			Number	Percent	Number	Percent	Number	Percent	Number	Percent
Methods involving special effort:										
Contact investigation	33	37.5	17		11		3		2	
Vigorous follow-up of lapsed cases	3	3.4	0		1		1		1	
Patient's initiative	32	36.4	7		5		17		3	
All other methods	20	22.7	6		4		6		4	
Total	88	100	30	34.1	21	23.9	27	30.7	10	11.4

[1] Negro cases with history of previous diagnosis and treatment of syphilis, current diagnosis of primary or secondary syphilis (reinfection or infectious relapse), and lesions visible to patient.

27 at the time of the present episode. Actually, only 17 of the original group of 32 cases that came to diagnosis through the patient's initiative did so again at the time of the subsequent appearance of syphilitic lesions. However, 10 cases which had previously been brought to diagnosis by other methods now came to attention through the patient's initiative. On the other hand, contact investigation and follow-up of lapsed cases, which had previously brought only 36 cases to treatment, located 51 cases in the present episode.

Discussion

In determining the relative effectiveness of the various case-finding technics, as demonstrated by the experience of health departments, special attention must be paid to the role of technics involving administrative or field effort directed toward selected individuals. These technics are considered more difficult to practice than routine and miscellaneous case-finding measures, such as serologic testing and educational programs. Having analyzed the experience of two health departments so far as newly discovered cases of syphilis were concerned, it was believed that it might be interesting and valuable to analyze a series of "repeaters" on a similar basis.

The 142 cases studied in this report had all received some treat-

ment for syphilis previous to the occasion on which a diagnosis of primary or secondary syphilis, either reinfection or relapse, was made; furthermore, each had one or more syphilitic lesions within his own range of vision. Informing a person of a diagnosis of syphilis is in itself an educational procedure of some importance which, at a very minimum, is accompanied by some statements about the disease and the enunciation of a few rules for the patient's future behavior. As seen in table 4, 131 cases (92.2 percent of the total) had been previously treated in the armed services, in rapid treatment centers, or in health department clinics. These agencies have specially designed educational programs for their patients, in which, among other things, the recognition of syphilitic lesions is discussed and the need for immediate diagnosis of suspicious lesions is stressed. On this basis, one might expect that the majority of the cases studied would have come to diagnosis through the initiative of the patient, since each has been taught to recognize syphilis as a possible cause of his visible, suspicious lesion.

Analysis of our data indicates, however, that such an expectation is not justified by our experience, since only 41.5 percent of the cases came in through the patient's initiative. Thus, the proportion of "repeater" cases that came to attention through the patient's initiative was virtually the same as the proportion (42.1 percent) of first episodes of infectious syphilis among Negroes that came in through the patient's initiative in the study reported previously (*1*). In the former study, also, it was found that contact investigation brought in 38.4 percent of the first episodes of infectious syphilis. This is to be compared with the fact that, in the group of "repeaters" analyzed in this report, contact investigation brought in 28.9 percent and the follow-up of lapsed cases brought in 15.5 percent, thus making a total of 44.4 percent located as a result of special efforts directed toward selected individuals. This is illustrated graphically in figure 2.

There is an interesting difference between the sexes in the effectiveness of case-finding methods. The patient's own initiative brought to diagnosis 57.1 percent of the male cases as compared with only 29.1 percent of the female cases. This is particularly interesting because each of these patients had a lesion visible to himself. This suggests that education aimed at raising the "level of suspicion" of the lay person as to the possibility of his lesion being due to syphilis was either not reaching females to the same degree as males, or that females have a greater tendency to ascribe visible suspicious lesions to causes other than venereal disease.

NEGRO

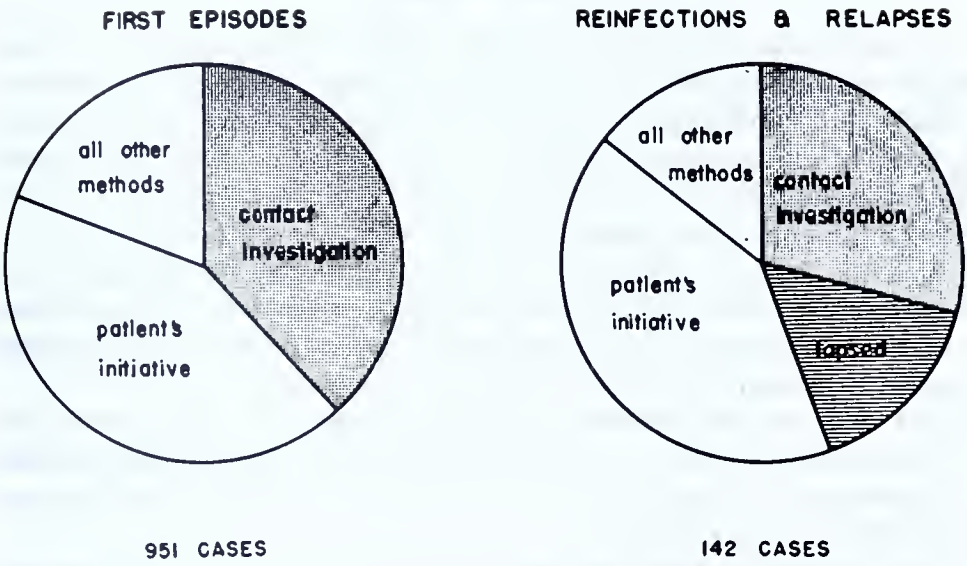


FIGURE 2.—Case-finding methods in infectious syphilis.

The data available in this analysis of cases of multiple episodes of infectious syphilis did not indicate any definite pattern of correlation between the various case-finding measures and such factors as the time interval since last treatment, the duration of the visible lesion, and the agency of previous treatment.

Reliable records indicating the case-finding method at the time of the previous diagnosis made possible a study of this factor in 88 cases (62 percent of the whole group). These data indicate that the patients who originally came to diagnosis on their own initiative could not be counted on to do so in subsequent episodes, since only 17 out of the original 32 came to diagnosis voluntarily in their later episodes. Furthermore, special efforts directed toward selected individuals (contact investigation and follow-up of lapsed cases) brought in a greater number of cases at the time of subsequent infection than on the occasion of the previous infection.

These data seem to indicate quite strongly that if special efforts in contact tracing and the follow-up of lapsed cases had been relaxed in the health department and reliance placed mainly upon the educational effect of previous treatment and its accompanying educational program, many of the cases of multiple episodes of infectious syphilis would have come to attention and control later than they did, if at all. It may be, of course, that syphilitic reinfection usually occurs in persons with a low receptivity to education. This explanation, however, would not apply to cases of relapse.

Conclusions

1. Accurate information on the relative effectiveness of the major case-finding measures in the discovery of cases of syphilitic relapse and reinfection is essential for the development and maintenance of an adequate syphilis control program. Such knowledge can be obtained by a careful analysis of the data relating to the case-finding methods which bring these cases to diagnosis.

2. This type of analysis of 142 Negro cases of primary or secondary syphilis (either reinfection or infectious relapse) covered a 4-year period in an urban health department in the southern United States and indicated that, in such cases:

(*a*) Special field efforts (contact investigation and active follow-up of lapsed cases) were responsible for bringing under control 44.4 percent of the cases while the patient's initiative was responsible for 41.5 percent.

(*b*) Special field efforts were most effective in the female cases, being responsible for bringing to diagnosis 49.4 percent of the total female group.

(*c*) In the male cases, the educational process, as evidenced by the proportion of cases which came in due to the patient's initiative, was the most important case-finding measure, being responsible for bringing to diagnosis 57.1 percent of the cases. Special field efforts were responsible for locating 38.1 percent.

(*d*) The fact that a patient came to diagnosis on his own initiative at the time of the previous syphilitic episode is not a reliable indication that he will again come to diagnosis on his own initiative when the lesions of a subsequent episode appear.

3. In terms of the relative effectiveness of various case-finding measures, the problem of discovering and bringing under control those individuals who have multiple episodes of infectious syphilis is essentially the same as that of discovering first infections.

Reference

1. Wright, J. J.; Sheps, C. G.: Reports of the North Carolina syphilis studies. I. An evaluation of case-finding measures in syphilis control. J. Ven. Dis. Inform., 30: 35–52, February 1949.

Studies on Syphilis in the Eastern Health District of Baltimore City

VIII. Reinfection and Relapse as a Component of the Discovery Rate [1]

Fred C. Kluth and W. Thurber Fales

Increasing use of rapid methods for the treatment of syphilis has given new significance to the role of reinfection and relapse in the epidemiology of syphilis. In the past, because the majority of patients failed to complete long-term schedules of treatment, reappearance of early syphilis was generally assumed to be a relapse of the original infection. Since the more recent rapid methods of treatment are practically always completed, the possibility that repeat episodes of early syphilis may be reinfections became apparent. As new sexual partners are frequently associated with these repeat episodes, examination of this interesting group of patients may reveal failure of application of known control measures or may lead to formulation of new and more effective ones.

Method of Study

The identification of two separate episodes of early syphilis in the same individual is relatively simple if sufficient clinical and serologic observations have been made. After treatment for syphilis, the reappearance of early manifestations of disease, the reversal of the trend of the titered serologic test from downward to upward, or the reappearance of relatively high-titer serologic tests after a period of negative or relatively low titer tests indicates the discovery of the new episode.

Unfortunately, in most individual cases a reliable differentiation between reinfection and relapse cannot be made, so no such differentiation was attempted here, all such episodes being included as newly discovered cases.

A list of discovered cases, as has been defined in previous papers of this series, was compiled from reports of cases to the Baltimore City Health Department and from reports of positive and doubtful tests at the laboratories of the Health Department and the Johns Hopkins Hospital. As physicians in private practice use the Health Department laboratories almost exclusively, very few cases coming to medical attention are omitted from this listing.

Though the years included in the Eastern Health District study extend back to 1932, the only prepenicillin year included here is

[1] From the School of Public Health, Johns Hopkins University.

1941, because only those cases coming to medical attention during 1941, 1946, 1947, and 1948 were specifically checked for the possibility of reinfection or relapse. The years 1942–45 were omitted because of extraordinary conditions associated with the war.

For the purposes of this paper all discovered cases were placed in two classes: (1) early syphilis, including primary, secondary and latent syphilis of less than 1-year duration; (2) all other syphilis, including latent syphilis of unknown duration, duration of more than one year, and symptomatic late syphilis.

Results

Discovery of Syphilis

Sixteen cases of early syphilis were discovered in white persons in 1941; the number discovered reached a peak, 93, in 1946, and decreased to 21 in 1948. For Negro persons similar changes in discovery occurred, a low number, 239, appearing in 1941, the peak, 550, appearing in 1946, and decreasing to 309 in 1948 (table 1). These figures clearly reveal the marked increase of discovery associated with the war and the rapid decline thereafter. Accurate population figures to calculate rates are not yet available, but it is known that the population of neither race has decreased to such an extent that the indicated trend would be altered.

Table 1.—*Discovered cases of syphilis; by duration of disease, race, and year of discovery, for all ages and both sexes; entire Eastern Health District; 1941, 1946, 1947, and 1948*

Year	Early syphilis (primary, secondary and latent of duration less than 1 year)		All other syphilis, (latent duration unknown, latent duration over 1 yr. and late)	
	Number	100 300 500	Number	100 300 500
WHITE				
1941	16		54	
1946	93		30	
1947	56		41	
1948	21		19	
NEGRO				
1941	239		350	
1946	550		241	
1947	444		238	
1948	309		185	

For all other stages of syphilis, the number of cases discovered in white persons dropped fairly consistently from 54 in 1941 to 19 in 1948, excepting a slight rise in 1947. For the Negro the drop again was consistent from 350 in 1941 to 185 in 1948. These

figures reveal a trend in discovery of this type of syphilis which was established some time before 1941.

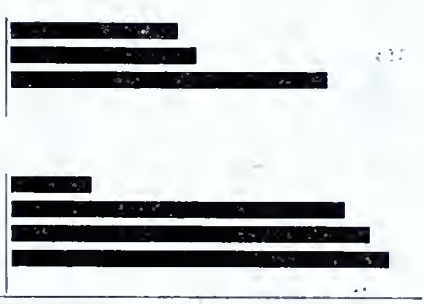
Discovery of Reinfection and Relapse by Race

Among discovered early syphilis cases in white persons in 1941, no cases were designated reinfection or relapse. In 1946, 11.1 percent of cases were so designated, and this percentage increased to 20.0 in 1948. For the Negro the percentage of cases designated reinfection or relapse was low, 5.5 percent in 1941. In 1946 it had reached the level of 22.7 percent and by 1948 had increased to 25.8 percent (table 2).

It is evident that persons having repeat episodes of early syphilis constitute a significant proportion of discovered early syphilis in both races for the years 1946 through 1948. As this high proportion does not appear in 1941, the increase is probably associated with the more widespread use of rapid treatment.

Table 2.—*Cases discovered as reinfection or relapse as a proportion of discovered early syphilis, by race and year of discovery for all ages and both sexes; entire Eastern Health District; 1941, 1946, 1947, 1948*

Year	Discovered cases with record of VD history	Cases discovered as reinfection or relapse	
		Number	Percent
WHITE			
1941	14	0	0.0
1946	72	8	11.1
1947	49	6	12.2
1948	15	3	20.0
NEGRO			
1941	200	11	5.5
1946	503	114	22.7
1947	420	104	24.8
1948	295	76	25.8



From these data the question arises, what portion of cases designated reinfection or relapse may actually be reinfection? The proportion of repeat episodes among Negro discovered cases of early syphilis, 1946 to 1948, was 22.5 percent, or about double the 10.6 percent found among white cases. We have no definite reason to doubt that the course of early syphilis in white and Negro persons is about the same and that the chance of relapse is the same. The proportion of relapse cases contributed each year to discovered cases in both races should then be about the same.

The observed difference between rates in the two races can be accounted for by reinfection, however, for the risk of infection of Negro persons is much higher than that of white persons. Similar deduction has been derived by Sternberg and Leifer, Schoch and Alexander, and Altschuler and co-workers from the study of cases given rapid treatment.

Among Negroes discovered in other stages of syphilis than early, the proportion apparently the result of relapse or reinfection was 0.3 percent in 1941, 8.6 percent in 1946, and 11.5 percent in 1948 (table 3). Among white persons in these stages of syphilis, very few such repeat episodes were found.

Table 3.—*Cases discovered as reinfection or relapse as a proportion of discovered syphilis, other than early (latent duration unknown, duration more than 1 year, and late); by race and year of discovery for all ages and both sexes; entire Eastern Health District; 1941, 1946, 1947, 1948*

Year	Discovered cases with record of VD history	Cases discovered as reinfection or relapse	
		Number	Percent
WHITE			
1941	45	1	2.2
1946	26	0	.0
1947	33	1	3.0
1948	15	1	6.7
NEGRO			
1941	320	1	.3
1946	210	18	8.6
1947	205	19	9.3
1948	165	19	11.5

Repeat Episodes According to Age

Distribution of discovered cases of early syphilis in Negroes by age (table 4) reveals a relatively young group for both sexes, younger in the female than in the male. Distribution of reinfection and relapse cases by age shows for both sexes a slightly older age distribution than that of all early cases. For white males, not shown in this figure, the age distribution of reinfection and relapse cases was also slightly older than that of all early syphilis cases. This table indicates that reinfection and relapse cases come from about the same age group as all early syphilis does, and that the two episodes in the same individual must occur within a year or so of each other.

Table 4.—*Age distribution by sex of all discovered early syphilis and cases discovered as reinfection or relapse; for Negroes, entire Eastern Health District; 3-year period, 1946-48*

Age	All early syphilis		Cases discovered as reinfection or relapse	
	Number	Percent	Number	Percent
MALE				
0–14	11	1.6	0	0.0
15–24	313	46.2	72	43.1
25–34	273	40.3	78	46.7
35–44	61	9.0	14	8.4
45 and over	20	2.9	3	1.8
Unknown	2		0	
Total	680	100.0	167	100.0
FEMALE				
0–14	36	5.8	4	3.2
15–24	371	60.1	72	57.1
25–34	169	27.4	43	34.1
35–44	32	5.2	4	3.2
45 and over	9	1.5	3	2.4
Unknown	6		1	
Total	623	100.0	127	100.0

Reinfection and Relapse by Occasion for Discovery

The distribution of cases of reinfection or relapse in Negroes of both sexes by occasion for discovery was approximately the same as that for all early cases (table 5). Though a large part of all discovery was the result of the patient's own initiative, there still remains a substantial proportion of relapse and reinfection cases which were discovered by routine examination. The repeat episode cases discovered by routine examination either acquired insufficient information at the initial episode or had insufficient motivation to seek re-examination. However, the relatively high proportion of voluntary visits in both Negro and white persons indicates that the patient's initiative probably can be further stimulated. (Data for white persons is not in this table.)

Reinfection and Relapse by Agency of Discovery

The distribution of cases of reinfection or relapse in Negroes of both sexes by agency of discovery (table 6) shows the venereal disease clinics taking a more prominent part in discovery of these cases than of all early syphilis. Private physicians, however, also take an important part in discovery of both types of cases. It is likely, though, that the improvident habits of most venereal disease patients make free medical attention essential to prompt discovery.

Table 5.—*Occasion for discovery of all early syphilis and early syphilis found as reinfection or relapse; by sex, for Negroes, all ages; entire Eastern Health District; 3-year period 1946-48*

Occasion for discovery—Sex	All early syphilis		Cases found as reinfection or relapse	
	Number	Percent	Number	Percent
MALE				
Voluntary with symptoms	225	33.1	57	34.1
Voluntary, no symptoms	9	1.3	3	1.8
Routine examination after prior syphilis	27	4.0	27	16.2
Routine examination with other V.D.	60	8.8	12	7.2
Routine examination as contact	69	10.2	14	8.4
Routine examination with medical complaint	51	7.5	5	3.0
Routine examination for physical fitness	41	6.0	12	7.2
Not stated (usually by physician)	198	29.1	37	22.1
Total	680	100.0	167	100.0
FEMALE				
Voluntary with symptoms	117	18.8	29	22.8
Voluntary, no symptoms	13	2.1	3	2.4
Routine examination after prior syphilis	33	5.3	33	26.0
Routine examination with other V.D.	20	3.2	7	5.5
Routine examination as contact	98	15.7	16	12.6
Routine examination with medical complaint	115	18.5	16	12.6
Routine examination prenatal	72	11.5	7	5.5
Routine examination for other physical fitness	26	4.2	3	2.4
Not stated (usually by physician)	129	20.7	13	10.2
Total	623	100.0	127	100.0

Table 6.—*Agency of discovery of all early syphilis and early syphilis found as reinfection or relapse; by sex, for Negroes of all ages; entire Eastern Health District; 3-year period 1946-48*

Agency of discovery—Sex	All early syphilis		Cases found as reinfection or relapse	
	Number	Percent	Number	Percent
MALE				
VD clinics	360	53.0	107	64.1
Physicians	176	25.9	29	17.3
Other clinics	73	10.7	11	6.6
Other agencies	71	10.4	20	12.0
Total	680	100.0	167	100.0
FEMALE				
VD clinics	274	44.0	90	70.9
Physicians	133	21.3	13	10.2
Obstetrical clinics	39	6.3	2	1.6
Other clinics	143	22.9	18	14.2
Other agencies	34	5.5	4	3.1
Total	623	100.0	127	100.0

Summary

Persons having repeat episodes of early syphilis constituted a significant proportion of all discovered cases of early syphilis in both whites and Negroes for the years 1946 to 1948, a greater proportion than that seen in the prepenicillin year of 1941.

The proportion of reinfection and relapse cases has been maintained at a relatively high level from 1946 to 1948, while the discovery of all early syphilis has dropped considerably.

Reinfection could be the origin of a large proportion of cases designated as reinfection or relapse, for reinfection is the most satisfactory explanation of the higher proportion of repeat episodes in Negro persons than in white.

As a practical measure of the risk of contracting infection in a population, all cases termed relapse may well be considered reinfection.

The group of cases discovered as reinfection or relapse may be representative of that portion of the population most likely to transmit venereal disease.

Unfortunately, individual instruction given to patients along with the experience with their original episode of syphilis, is still insufficient to prevent a substantial portion of reinfection or to instill the desire voluntarily to seek medical assistance.

Venereal disease clinics, probably because they are free of charge, are used by the largest portion of patients for discovery of both original and repeat episodes of early syphilis.

The Frequency of Discovery of Syphilis in Up-State[1] New York Between 1936 and 1943[2]

William H. Haenszel and James H. Lade

While the prevalence of all stages of syphilis is a measure of effectiveness of control measures applied to the preceding generations, incidence measures the success of present programs. Serologic surveys may yield information concerning prevalence in proportion to the adequacy of coverage of the population concerned, but little information concerning the incidence of new cases can be thus secured. The difference in prevalence between residents

[1] New York State exclusive of New York City.

[2] From the New York State Department of Health.

of geographical areas, ages, races, and between permanent residents and transients make a survey sample representative of the population very difficult to attain. But were these difficulties surmounted, surveys could not yield information concerning new cases as they occur.

Although case reporting yields information in reference to incidence which cannot be secured by survey methods, it is subject to the following defects:

1. Incomplete coverage because of infected persons who do not seek medical attention.
2. Variations in discovery rates produced by fluctuations in the number and type of physicians serving the population.
3. Duplication in counting cases resulting from the use of false names on case reports.

Case report statistics, therefore, should be supplemented by methods which estimate the degree to which cases are reported as they occur. Such an estimate can be derived from a comparison of case reports collected in up-State New York from 1936–43 [3] with Selective Service serologic reports. The system of collection of case reports in up-State New York has been completely described elsewhere (*1*). For the purposes of this paper, it may be sufficient to say that all laboratories performing serologic tests for syphilis are required to transmit a copy of each report which is not negative to the health officer of jurisdiction. Case reports are secured, specific as to stage of disease, by name of patient for 97 percent of persons thus known to have a serologic reaction. While physicians may report cases by initials and date of birth, only 1 percent are reported in this way.

Examination of Male Population by Selective Service

Arrangements were made for the State Department of Health to receive copies of serologic reports for all prospective draftees examined by local examining boards or at Army induction stations. One copy was forwarded to the United States Public Health Service which undertook the task of eliminating duplicate serologic reports and of counting the total number of males examined and determining the prevalence of syphilis as revealed by serologic reactions.

During this period, laboratory service for the examination of specimens collected in the course of Selective Service examinations was provided by the State Health Department and a few of the larger municipal laboratories, and the tests performed were iden-

[3] Except for Buffalo and Rochester where case reporting began in 1918 and 1920 respectively.

tical with those upon which physicians based their diagnoses in private practice. There was some change in the serologic technics between 1936 and 1943, but the sensitivity and specificity were not greatly affected.

Reports have been released by the Public Health Service concerning males examined in up-State New York from November 1940 to August 1941, but no count of examinations after that period was ever made available. An estimate of the number of selectees examined during the 38-month period from November 1940 to December 1943 has been prepared by dividing the number of seropositive individuals found during that time by the prevalence rates for the various age groups established in the period from November 1940 to August 1941. The results were checked with other information (local board quotas for induction calls, age distribution of men in the Army, etc.) and the estimates seemed sufficiently accurate, particularly for ages under 35 years, to warrant their presentation in this paper, although the actual count of the number examined would, of course, have been preferred. The estimated number of persons under 35 years examined by Selective Service and the percent it formed of the 1940 census population has been given in table 1. It appears that approximately 63 percent of all men between 18 and 34 in up-State New York had been examined at some time between November 1940 and December 1943. The completeness of coverage was greater for the younger ages, ranging from 88 percent for the 18–19 year group to 42 percent for men 30–34 years.

Table 1.—*Estimated number and percent of males examined by Selective Service, Up-State New York, November 1940 to December 1943*

Age as of 1943 (years)	Number	Percent of male population: 1940 census
18–34	514,000	63
18–19	93,500	88
20–24	185,300	75
25–29	139,200	60
30–34	96,000	42

Because of the relatively incomplete coverage of men 35 years and over and the possibility of obtaining unrepresentative samples in those age groups through the operation of deferments for dependency and occupation, much of the discussion in this paper has been confined to men under 35 years. It should be pointed out that this paper is not concerned with prevalence of syphilis. This

subject has been covered by the Public Health Service reports.[4] For the purposes of this paper a representative cross section of persons infected with syphilis is needed so that they can be checked to see whether they have been previously reported as a case.

Another reason for restricting discussion to males under 35 years is that for most of up-State New York a syphilis case reporting system has been in operation only since 1936. To include persons over 35 years would lead to an unduly low estimate of the frequency of discovery of syphilis since the inception of the present case reporting system, because of the greater probability of the completion of treatment prior to 1936 in this age group.

Frequency of Discovery of Syphilis

The 14,362 selectees found to have a serologic reaction for syphilis constitute the index cases for this study. Of these, 691 were excluded because they were transients or because they were later found definitely not to be cases of syphilis. Another 2,864 were also eliminated because they had doubtful reactions of low titer, and might not have been infected with syphilis, leaving 10,807 seropositive reactors of whom 6,191 were under 35 years of age when examined.

An obvious measure of completeness of discovery is the proportion of seropositive selectees identified in the case report file as previously reported cases of syphilis. Table 2 presents this comparison. Out of a sample 6,191 seropositive selectees aged 18 to 34 years, 2,577 or 41.6 percent were known to have been reported

Table 2.—*Selectees 18 to 34 years with a positive serologic reaction for syphilis reported as a case prior to selective service examination according to race*

[Up-State[1] New York, November 1940 to December 1943]

	Total			White			Nonwhite		
	Number of seropositive sclectees	Previously reported		Number of seropositive selectees	Previously reported		Number of seropositive selectees	Previously reported	
		Number	Percent		Number	Percent		Number	Percent
Up-State[1] New York, total	6,191	2,577	41.6	3,983	1,653	41.5	2,208	924	41.8
Buffalo	741	438	59.1	362	216	59.7	379	222	58.6
Rochester	190	119	62.6	158	99	62.7	32	20	62.5
Rest of up-State[1] New York	5,260	2,020	38.4	3,463	1,338	38.6	1,797	682	38.0

[1] New York State, exclusive of New York City.

[4] Results of Serological Blood Tests for Syphilis on Selective Service Registrants. Federal Security Agency, Washington, D. C., 1941.

previously as a case. This is a minimum estimate, for it is based on the number of successful searches and takes no account of failures in searching. Names in the case report file were arranged both in soundex order and geographical order. Names could be located and matched despite variations in spelling and mechanical problems of filing can be ignored as a source of error in the results. This would leave 58.4 percent of the seropositive selectees not reported previously as cases.

Data for Buffalo and Rochester are presented separately in table 2 because their case reporting systems antedated considerably that of the rest of the up-State area, Rochester's system having been established in 1920, and Buffalo's in 1918. A total of 154 seropositive selectees 18 to 34 years of age were identified as cases reported prior to 1936 in Buffalo and Rochester. It will be seen in table 3 that persons over 35 years of age were identified with even greater frequency in the files of these cities than for the rest of up-State New York.

There is a striking difference in the percentage of seropositive selectees 18 to 34 years of age previously reported as cases in Buffalo (59.1 percent) and Rochester (62.6) and the percentage for the rest of up-State New York (38.4). The reason for this difference appeared to be the greater age of the files in Buffalo and Rochester, for when the seropositive selectees identified as reported prior to 1936 were subtracted, the proportion of cases reported prior to Selective Service examination in these cities was similar to that of the rest of the State. It is of interest to note that in each of the three areas no significant difference by race was observed.

Proportion of Cases Known to Have Been Reported Previously, by Age and Color

For that portion of up-State New York, exclusive of Buffalo and Rochester, where case reporting was begun in 1936, the proportion of selectees reported as cases prior to Selective Service examination did not vary markedly by age or race. The somewhat lower rates of discovery for persons 40 years and over may have been due to diagnosis prior to 1936 and termination of treatment and serologic testing prior to establishment of the case roster, while those for selectees under 20 years may be related to the shorter time period for the discovery of their infections. In Buffalo and Rochester the rate of discovery prior to Selective Service examination exceeded that of the rest of the up-State New York by an even greater margin in the ages over 35 than that previously noted for the 18–34 age group. This difference was clearly due

Table 3.—*Selectees with positive serologic reaction for syphilis reported as a case prior to selective service examination according to age and race*

[November 1940 to December 1943]

(Up-State[1] New York)

Age at time of selective service examination (years)	White			Nonwhite		
	Number of seropositive selectees	Reported as a case prior to selective service examination		Number of seropositive selectees	Reported as a case prior to selective service examination	
		Number	Percent		Number	Percent
All ages [2]	7,431	2,969	40.0	3,376	1,423	42.2
18–19	272	98	36.0	120	39	32.5
20–24	823	346	42.0	502	211	42.0
25–29	1,075	477	44.4	639	261	40.8
30–34	1,813	732	40.4	947	413	43.6
35–39	1,718	684	39.8	695	308	44.3
40 and over	1,574	605	38.4	449	186	41.4
Buffalo and Rochester, with case report files antedating 1936						
All ages [2]	1,028	645	62.7	675	405	60.0
18–19	23	9	39.1	23	13	56.5
20–24	95	51	53.7	92	52	56.5
25–29	162	104	64.2	115	67	58.3
30–34	240	151	62.9	181	110	60.8
35–39	226	146	64.6	162	102	63.0
40 and over	270	179	66.3	95	58	61.1
Up-State [1] New York, exclusive of Buffalo and Rochester						
All ages [2]	6,403	2,324	36.3	2,701	1,018	37.7
18–19	249	89	35.7	97	26	26.8
20–24	728	295	40.5	410	159	38.8
25–29	913	373	40.9	524	194	37.0
30–34	1,573	581	36.9	766	303	39.6
35–39	1,492	538	36.1	533	206	38.6
40 and over	1,304	426	32.7	354	128	36.2

[1] New York State, exclusive of New York City.
[2] Includes "age not stated."

to the greater number of years the files in those cities had been maintained.

Positive serologic tests discovered as a result of premarital examinations made in the years 1939–41 in up-State New York (exclusive of Albany, Buffalo, Rochester, and Syracuse) have been analyzed in a similar manner. Out of 595 seropositive males 175 or 29.4 percent were found to have been previously reported. The corresponding figures for females were 585, 181, and 30.9 percent, respectively. The available evidence does not indicate any pronounced sex difference.

Use of Pseudonyms on Case Reports

The question arises as to how many additional selectees had been reported as cases, but were not so identified by the means at hand. In this connection the use of pseudonyms by patients or physicians, leading to failure to match case reports with the true name on the Selective Service serologic reports must be considered.

For this purpose the mails were used to verify the names used on case reports in 1947 and 1948. Questionnaires framed as an opinion poll on public health information were sent by registered letters to persons reported as cases and a receipt of delivery secured from the post office. The illness of the addressees was in no way mentioned or implied. The presumption was that delivery of a registered letter would constitute substantial proof that the patient's correct name had been given on the case report. To test this assumption 19 letters were mailed, 10 addressed fictitiously both as to name, street and house number, and 9 with fictitious name and address known to exist. The post office did not report nondelivery or removal of the addressee for any of these letters.

Quotas based on the volume of case reports received from the various up-State municipalities were used as a guide to the distribution of the first 200 letters; another 432 letters were sent as case reports were received without selection or omission until the desired number was attained. However, subsequent analysis revealed no significant difference in the findings of the two samples. The results are presented in table 4 for 628 letters.

Table 4.—*Veracity of names and addresses on case reports as indicated by delivery of registered letters to persons reported in 1947 and 1948*

[Up-State[1] New York]

	Total			White	Nonwhite
	Both sexes	Male	Female		
Number of letters sent	628	343	285	385	243
Letters delivered:					
Number	537	293	244	339	198
Percent	85.5	85.4	85.6	88.0	81.5
Addressee moved:					
Number	28	13	15	11	17
Percent	4.5	3.8	5.3	2.9	7.0
Letters unclaimed; addressee unknown; no such address:					
Number	63	37	26	35	28
Percent	10.0	10.8	9.1	9.1	11.5

[1] New York State, exclusive of New York City.

A total of 537 letters or 85.5 percent were delivered. An additional 4.5 percent of the addressees were stated to have moved. If these dispositions may be taken as evidence that the addressees were known by the names given on the case report, the sample investigated would permit the inference that 90.0 percent of the cases reported in 1947 and 1948 were accurately identified. Failure to deliver some proportion of the 10 percent "unclaimed, unknown, no such address" may have resulted from misunderstanding of the address or incomplete notation of address by the physician, particularly for patients seen only once. Though such letters could not be delivered, the name, age, sex, and color on some of the corresponding case reports could have been accurate enough to permit matching with a Selective Service report. It would appear that something more than 90 percent of the 1947–48 case reports bore the true name of the patient.

It must be acknowledged, however, that a general improvement in case reporting practices among physicians in up-State New York did occur between 1936 and 1948. No information is available on the extent of this improvement, but there is no evidence that the use of pseudonyms on case reports in the years 1936–43 was common.

An adjustment of the observed proportion of seropositive selectees previously reported as a case to take account of this factor would not in our opinion materially alter the conclusions to be drawn from the results.

To summarize the findings so far, 40.6 percent of men seropositive at the time of Selective Service examinations in up-State New York had been reported as cases prior to examination. Without respect to stage of disease as originally reported, this proportion appeared to hold for the range 18 to 40 years and for whites and nonwhites and, so far as could be determined, for females also.

Cases Reported in the Early Stage

No reference has been made in the preceding sections to the elapsed time between date of onset and date of report. The fundamental principle of syphilis control is the detection and treatment of cases in the early or infectious stage and for this reason an estimate of the proportion discovered, reported, investigated for contacts and treated within a year of onset is of particular interest. Since stage of disease is part of the information included on the case report, it is possible to analyze the material in this manner.

This phase of the investigation was restricted to males under

25 years at the time of examination, practically all of whom must have contracted the disease, barring congenital infections, subsequent to 1936 when the present system of case reporting was started. According to table 3, there were 1,717 selectees in this age group. Information on stage of disease for these selectees indicated that 396 were cases of congenital syphilis, leaving 1,321 cases of acquired syphilis for consideration. Of these, 175 or 13.2 percent [5] were found to have been reported in the early stage prior to Selective Service examination. This figure may be compared with 40.4 percent in this age group found to have been reported at any stage of the disease prior to Selective Service examination.

Among these young males the possibility that some cases reported as late syphilis were unrecognized early cases must be kept in mind. Turner, Dyar, Clark, and Birkhead (*2*) in their Baltimore study were of the opinion that most of the reported late cases in this age group were really early cases (duration of infection less than 1 year). This would seem to be an extreme position when one recalls the relatively short time after infection in which a case can be reported as early. The fact that 139 early cases (half of which were in the primary and secondary stage) in this age group were discovered by routine Selective Service examination, would clearly indicate that discovery of early syphilis had been far from complete, for only 175 early cases had been discovered prior to examination.

The marked difference in discovery rates for cases of all stages in Buffalo and Rochester previously cited, suggested a similar inquiry into the discovery of early syphilis. In the two cities 23.8 percent of seropositive selectees under 25 years had been reported as early syphilis prior to Selective Service examination, more than double the proportion observed in the remainder of up-State New York, 11.4 percent.

Application of Method

In arranging for a serologic survey to be collated with a case report file which includes all cases known to any physician, the surveyed population must be selected in a manner uninfluenced by the probability of a previous case report.

This criterion would rule out mass blood-testing programs for the detection of syphilis which depend on the cooperation of the

[5] Since some of the 139 selectees reported as early cases as a result of Selective Service examination might have been discovered later as early cases by other means, there would be some ground for omitting them from consideration in computing the percentages. If this is done, the figure of 13.2 percent would be raised to 14.8 percent.

public, but would permit the use of premarital and prenatal examinations and the routine collection of serologic specimens incidental to studies mainly directed to other objectives, such as tuberculosis X-ray surveys.

The effectiveness of measures of control must be assayed in the light of information concerning the apparent proportion of existing cases to which such measures can be applied.

Conclusions

A method of collating case reports with serologic survey material, as applied to Selective Service data for up-State New York has been described.

1. Of males 18 to 34 years found to have a positive serologic reaction in the course of the Selective Service examination, 40.6 percent had been reported as cases of syphilis in up-State New York between 1936 and 1943.

2. Thirteen and two-tenths percent of seropositive selectees under 25 years of age had been reported during the first year of their infection.

3. In Buffalo and Rochester, the percentage of cases reported prior to Selective Service examination was well in excess of the rate in the rest of the up-State area, with respect to early syphilis as well as the later stages.

References

1. Brumfield, W. A., Jr.; Lade, J. H.; Feldman, L. L.: The epidemiology of syphilis based upon five years' experience in an intensive program in New York State. Am. J. Pub. Health, 32: 793, 1942.
2. Turner, T. B.; Dyar, R.; Clark, E. G.; Birkhead, M. F.: Studies on syphilis in the Eastern Health District of Baltimore City. II. Discovery rates as an index of trend. Am. J. Hyg., 37: 273, 1943.

An Evaluation of Case-Finding Measures in the Control of Gonorrhea[1]

John J. Wright and Cecil G. Sheps

Introduction

In previous communications, (*1*, *2*) the authors have discussed the importance of careful evaluation of the effectiveness of case-finding measures in syphilis control. The organization and field of operation of the North Carolina Syphilis Studies have been described.[1] Although these studies have been devoted to syphilis incidence and prevalence and its control program, it was possible, in addition, to arrange for careful records to be kept relating to certain aspects of the cases of gonorrhea which came to the attention of the health department. The purpose of this paper is to report on an analysis of the origin of 2,061 cases of gonorrhea in order to determine the relative effectiveness of the major case-finding procedures in gonorrhea control in an urban area served by a health department carrying on an average type of venereal disease control program. Also reported is an analysis of the results of the investigation of 1,015 consecutive contacts of gonorrhea.

Method of Study

The data presented in this communication include all the patients with gonorrhea diagnosed at the Durham City and County Health Department during the period January 1, 1946, through June 30, 1948, who were interviewed with a view to determining, among other things, the factor responsible for bringing each patient to diagnosis.

Criteria for diagnosis were based upon reliable positive findings in at least two of the following fields: Clinical and epidemiologic history, physical findings, and laboratory examinations including cultures and fermentation tests.

A number of individuals were included more than once because they were diagnosed as having had one or more gonorrhea reinfections. In addition to clinical findings the following criteria were used in making a diagnosis of gonorrhea reinfection:

(*a*) Females—A period of at least 6 months since previous diagnosis or a shorter period, provided that there had been at least 3 negative cultures with menstrual periods intervening.

[1] From the School of Public Health, University of North Carolina. This study was supported jointly by grants from the International Health Division of the Rockefeller Foundation and the N. C. State Board of Health.

(*b*) Males—No time consideration, clinical basis only.

An analysis of the results of the investigation of all the contacts of gonorrhea reported to the health department for the year 1947 is also included. This group was comprised of contacts about whom information was obtained in the health department itself and also those who were reported from outside its jurisdiction.

Classification of Origin of Cases

The classification used is a functional one in terms of what brought the patient to recognition as a case of gonorrhea, regardless of the referral agency. The case-finding procedures which brought these cases to attention fall into three groups, each of which requires quite different activities on the part of the health department:

1. Epidemiology or contact investigation—administrative and field effort directed toward selected individuals.
2. Voluntary application or the patient's initiative—the result of educational effort directed toward groups which may or may not be selected.
3. All other methods—routine, premarital, prenatal, food handlers, suspect, military, etc.

Classification of Results of Contact Investigation

There are two classes: those contacts who were not located and those who were. The primary reasons for not locating contacts were insufficient or incorrect identifying information or that the contact had moved outside the jurisdiction of this health department. The contacts who were located were grouped as follows:

1. Gonorrhea present and brought to treatment.
2. Already under treatment for gonorrhea.
3. Negative for gonorrhea.
4. Failed to complete examination.

Analysis of Data

The data for the interviewed cases of gonorrhea were classified and tabulated according to the following characteristics:

1. Origin of case—by case-finding procedure.
2. Race.
3. Sex.

The data relating to the results of investigation of contacts of gonorrhea were classified and tabulated as follows:

1. Disposition of case.
2. Race.
3. Sex.

The tables present the data which are discussed. It will be noted that in some instances the percentages do not add up to precisely 100 percent. These differences in summation are due to rounding.

Results of Study

A total of 2,061 cases of gonorrhea diagnosed in the health department in the 30-month period ending June 30, 1948, were analyzed. The actual number of cases of gonorrhea diagnosed during that time was greater because it was not possible to interview all patients due to insufficiency of personnel. Table 1 shows the distribution of cases diagnosed and cases interviewed, and thus included in this study, by race and sex. It is seen that 69.2 percent of the patients were interviewed. Since, under the pressure of work it was not possible to interview all, choices would be made by the clinic staff on the following basis:

Table 1.—*Cases of gonorrhea diagnosed and interviewed—by race and sex*

Race and sex	Cases of gonorrhea		Cases interviewed	
	Number	Percent	Number	Percent
Negro:				
Male	1,725	58	1,289	62.5
Female	914	30.7	546	26.5
White:				
Male	220	7.4	172	8.3
Female	117	3.9	54	2.6
Total	2,976	100	2,061	100

1. Included at all times—sulfa-resistant cases prior to the administration of penicillin
2. Omitted when necessary—
   (*a*) Patients deemed to be uncooperative.
   (*b*) Wives of known infected males.

Only one of these factors, 2 (*b*) (wives of known infected males), creates a bias in favor of interviewing more male cases than female. This probably accounts for the fact that a somewhat greater proportion of the male cases than females was interviewed in the health department studied.

Origin of Cases by Race and Sex

Table 2 and figure 1 show the origin of all cases by race and sex. From the point of view of race differences, attention is drawn to the fact that among the white cases a higher proportion came to

Table 2.—*Origin of cases of gonorrhea, by race and sex*

Origin of case	Negro				White				Total	
	Male		Female		Male		Female			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Contact investigation	78	6	399	73	2	1.2	32	59.2	511	24.8
Patient's initiative	1,177	91.3	76	13.9	169	98.2	16	29.6	1,438	69.8
All other methods	34	2.6	71	13.0	1	.6	6	11.1	112	5.4
Total	1,289	100	546	100	172	100	54	100	2,061	100

diagnosis on their own initiative in both sexes than in the Negro cases, the proportions being white male, 98.2 percent, as against Negro male, 91.3 percent; and white female, 29.6 percent, as against Negro female, 13.9 percent.

A very striking difference is obvious in the relative effectiveness

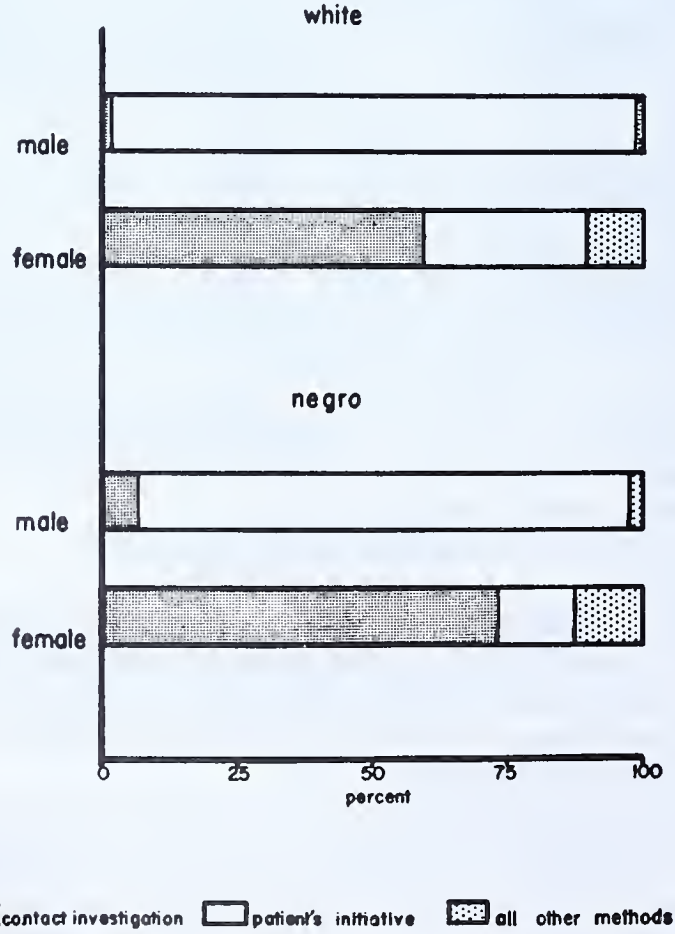


FIGURE 1.—Origin of cases, by race and sex.

of the major case-finding procedures between the sexes in both races. In Negro males contact investigation was responsible for only 6 percent of the cases and the patient's initiative for 91.3 percent, whereas in Negro females the respective proportions were 73 percent and 13.9 percent. In white males, contact investigation was responsible for 1.2 percent and the patient's initiative for 98.2 percent, whereas in white females the respective proportions were 59.2 percent and 29.6 percent.

The distribution of case-finding procedures as described in this section was found to be highly significant statistically.[2]

Results of Contact Investigation by Race and Sex

Table 3 and figure 2 show the results of investigation of gonorrhea contacts by race and sex. The data analyzed include only those contacts which were located. There were an additional 204 contacts reported in the year who were not located. Thus, the group analyzed here represents 83.3 percent of all the gonorrhea contacts reported to this health department in 1947.

Table 3.—*Results of investigation of gonorrhea contacts, by race and sex*

Result of investigation	Negro				White				Total	
	Male		Female		Male		Female			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Brought to treatment	51	13.1	329	58.2	0	0	23	63.9	403	39.7
Already under treatment	194	49.9	123	21.8	13	52.0	6	16.7	336	33.1
Not infected	134	34.4	106	18.8	11	44.0	6	16.7	257	25.3
Incomplete examination	10	2.6	7	1.2	1	4.0	1	2.7	19	1.9
Total	389	100	565	100	25	100	36	100	1,015	100

In tabulating the disposition of the contacts who were reported more than once during the same period and who were brought to treatment by the investigation, they were counted once as being "brought to treatment" and subsequently as "already under treatment." It is pointed out also, that this analysis as to results of investigation refers to gonorrhea only and does not take into account other venereal diseases, since the aim was to assess the value of the investigation of gonorrhea contacts as a gonorrhea case-finding measure.

The data demonstrate a very marked sex difference in the pro-

[2] Grateful acknowledgment is made to the Institute of Statistics, Greater University of North Carolina, for assistance with this phase of the analysis.

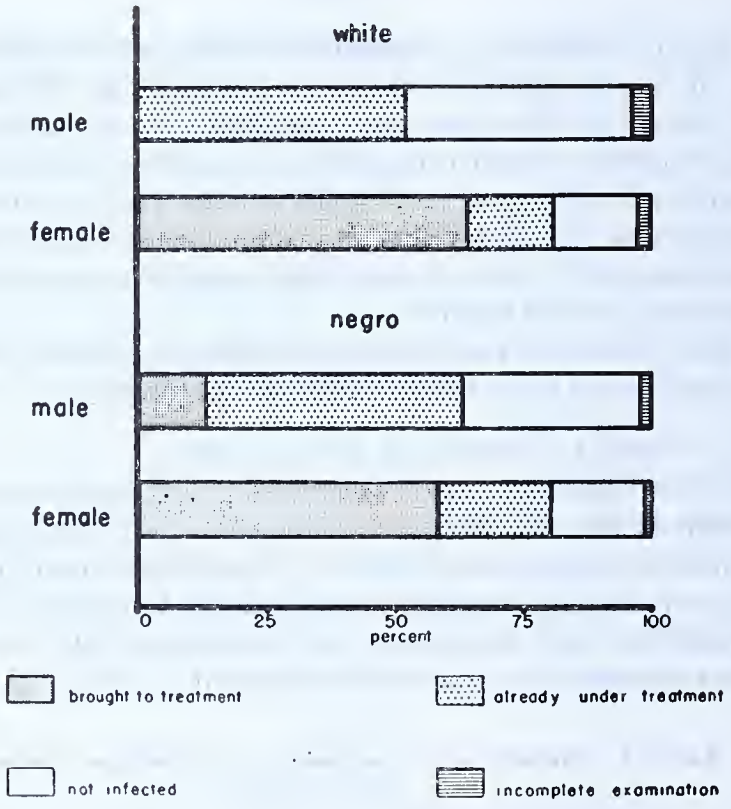


FIGURE 2.—Results of investigation of gonorrhea contacts.

portion of contacts brought to treatment as a result of the investigation. This is true in both races. Thus the proportion of Negro male contacts brought to treatment was 13.1 percent as compared with 58.2 percent for Negro females. This sex difference was very significant statistically. The comparable proportions for the white contacts, though much smaller in number, are very similar in their distribution.

A similarly striking, statistically significant, sex difference is seen in the proportion of contacts in both races found, on investigation, to be already under treatment for gonorrhea. Thus, the proportion of Negro male contacts already under treatment was 49.9 percent as compared with 21.8 percent for Negro females. For the white contacts the comparable proportions were: males, 52.0 percent and females, 16.7 percent.

In both races also a statistically significant sex difference was observed between the proportion of contacts found to be free of gonorrheal infection. Thus, the proportion of Negro male contacts who were not infected was 34.4 percent as compared with 18.8 for Negro females. The comparable proportions for the white contacts were: males, 44.0 percent and females, 16.7 percent.

Discussion

The effectiveness of penicillin in the treatment of gonorrhea has simplified the problem of gonorrhea control by reducing the importance of case holding. This development, however, serves to emphasize the importance of case finding. Careful studies are therefore needed to evaluate the relative effectiveness of the major case-finding technics in gonorrhea control in order to provide a basis for finding the administrative compromise which is necessary between effectiveness and economy. This is of particular importance with reference to the evaluation of contact investigation because it may be expected that an increasing proportion of gonorrhea cases will be treated by private practitioners. If serious attempts are to be made to develop the use of this epidemiologic approach with private patients, it behooves us to be reasonably certain of the value of such a program.

The literature which sheds some light on this matter is largely confined to analyses of health department data with a view to determining how many new cases of gonorrhea are found per original patient (*3*) or per contact named (*4*). It is probable that studies of that type form the basis of the statement made by Gillis (*5*) in 1948, "The experience gained during the war proved that investigation of gonorrhea contacts is one of the most difficult, expensive, and variable phases of venereal disease control." While this statement may on the whole be true, it would appear from our analysis that there are certain segments of this problem in which contact investigation plays a more reliable and vital role than in others.

When the data relating to the origin of cases of gonorrhea are broken down on a race- and sex-specific basis, reliable and useful information is obtained. In this connection it is pointed out that, in this health department, equal effort was exerted in the follow-up of both male and female contacts. In actual practice, the investigators, before proceeding with their daily activities, would sort out their contact slips on the basis of geographic proximity without any regard to the sex of the contact. There is a striking difference in the effectiveness of contact investigation between the sexes. It is responsible for bringing to recognition 73 percent of the Negro females and 59.2 percent of the white females. The role of contact investigation in males was much less important, providing only 6 percent of Negro cases and 1.2 percent of white cases.

Our data also indicate that the patient's initiative is somewhat more reliable as a case-finding measure among whites than among

Negroes. This was responsible for bringing to diagnosis 98.2 percent of the white males as against 91.3 percent of Negro males and 29.6 percent of white females as compared with 13.9 percent of Negro females.

These data indicate quite clearly that if this health department had relaxed its efforts in contact investigation, more than half of the female cases of gonorrhea would have come to attention and control later than they did, if at all. This suggests that educational effort aimed at raising the "level of suspicion" of the lay person as to the possibility of urogenital symptoms being due to gonorrhea was either not reaching females to the same degree as males, or that females have a greater tendency to ascribe such disturbances to causes other than venereal disease.

The analysis of data relating to the results of contact investigation indicates that there is a very striking difference, on a sex-specific basis, in the effectiveness of this procedure as a case-finding measure in the control of gonorrhea. This is of some importance from the administrative point of view. It is seen that among the Negro contacts for example, more females were infected (80 percent) than males (63 percent). Furthermore, of the infected females, almost three-quarters (72.8 percent) were not under treatment when investigated, whereas, of the infected males, less than one quarter (20.8 percent) were not under treatment when investigated. Expressed somewhat differently it might be said that these data indicate that for every 100 female contacts located, 58.2 cases of gonorrhea were brought under control, whereas, for every 100 male contacts located, only 13.1 cases were brought under control—a ratio of somewhat more than 4 to 1. The comparable proportions for the white contacts, though the numbers involved are much smaller, are very similar.

Conclusions

1. Accurate information on the relative effectiveness of the major case-finding measures in the discovery of new cases is essential for the development and maintenance of an adequate gonorrhea control program. Such knowledge can be obtained from a careful analysis of the data relating to the origin of such cases with special attention being paid to sex differences. This type of analysis of 2,061 cases of gonorrhea diagnosed in an urban health department in the southern United States indicates that:

(*a*) Contact investigation was responsible for bringing to diagnosis the greatest proportion of female cases.

(*b*) The patient's initiative was responsible for bringing to diagnosis the greatest proportion of male cases.

(*c*) Educational effort, as evidenced by the proportion of cases coming to attention on the patient's initiative in the period studied, was more effective among whites than among Negroes.

2. Valuable information on the effectiveness of contact investigation as a case-finding measure in the discovery of untreated cases of gonorrhea can be obtained by analyzing the results of such activity on a sex-specific basis. This type of analysis of the disposition of 1,015 gonorrhea contacts who were located indicates that:

(*a*) A greater proportion of female contacts than males was found to be infected.

(*b*) Of those who were infected, a much greater proportion of the males than females was found to be already under treatment.

(*c*) The number of previously untreated cases of gonorrhea brought under control as a result of the investigation of 100 female contacts was more than 4 times the number of such cases resulting from the investigation of 100 male contacts.

Acknowledgment

The authors wish to express appreciation to the Superintendent of the Durham City and County Health Department and the Director and Staff of its Venereal Disease Clinic whose cooperation made this study possible.

References

1. WRIGHT, J. J.; SHEPS, C. G.: Reports of the North Carolina syphilis studies. I. An evaluation of case-finding measures in syphilis control. J. Ven. Dis. Inform., 30: 35–52, February 1949.
2. WRIGHT, J. J.; SHEPS, C. G.: Reports of the North Carolina syphilis studies. II. An evaluation of case-finding measures in multiple episodes of infectious syphilis. J. Ven. Dis. Inform., 30: 187–194, July 1949.
3. GUTHRIE, N. W.: Contact investigation in gonorrhea. Am. J. Syph., Gonor. & Ven. Dis., 28: 571, September 1944.
4. ELLIOTT, G. R. F.; BEATTIE, J. A.; WYNESS, E. S.; GILLEY, J. R.: Some recent developments in venereal disease epidemiology in British Columbia. Can. J. Pub. Health, 39: 235, June 1948.
5. GILLIS, E. A.: Gonorrhea control during the decade of World War II. Am. J. Syph., Gonor. & Ven. Dis., 32: 99, March 1948.

Penicillin in the Abortive Treatment of Syphilis[1]

Frederick Plotke, Henry Eisenberg, Amelia H. Baker, and M. E. Laughlin

It is obvious that an effective method for preventing syphilis in persons known to have been exposed would be of great value in the control of this disease. Therefore, an investigation of the prophylaxis of syphilis has been carried on in one of the venereal disease clinics of the Chicago health department to try to determine whether or not the incidence of subsequent syphilis in a group of contacts of infectious syphilis treated with 600,000 units of penicillin in peanut oil and beeswax (Romansky formula) would show any significant difference from a control group of untreated contacts. This investigation covered a period of 1 year, August 25, 1947, to August 24, 1948, and a 6-month period of follow-up on all cases. This study was initiated upon the request of Dr. Harry Eagle[2] who was collaborating on a similar study with the Baltimore Department of Health.

Eagle, Magnuson, and Fleischman (*1*) had reported that relatively small doses of penicillin are required during the incubation period of syphilis to abort the development of the disease in rabbits.

Alexander and Schoch (*2*) have employed a "1-day abortive cure" treatment consisting of 900,000 units of calcium penicillin in oil and beeswax, plus 120 mg. of bismuth plus 0.05 to 0.06 gm. arsenoxide given intravenously. Among 115 contacts who received this abortive treatment, 6 developed early syphilis. One hundred and thirty contacts were observed untreated, and 54, or 41.5 percent remained negative, while 75, or 58.5 percent, developed syphilis.

Method of Study

All named sexual contacts of primary and secondary syphilis patients were considered potential study cases.

Sexual contacts were persons who were reported to have had intercourse with a syphilitic patient at any time during the 3-month

---

[1] From the Venereal Disease Control Program, Chicago Board of Health, in cooperation with the U. S. Public Health Service. Under the direction of Herman N. Bundesen, Senior Surgeon (R) (Inactive), U. S. Public Health Service; President, Chicago Board of Health.

[2] Then Senior Surgeon of the U. S. Public Health Service, Medical Officer in Charge, Laboratory of Experimental Therapeutics, Johns Hopkins School of Hygiene, Baltimore.

period prior to the patient's onset of primary syphilis, or 5 months prior to the appearance of secondary symptoms.

When the full name and address of these contacts were known they were sent telegrams asking that they report immediately to the Director of the Epidemiology Section. In instances in which sufficient information to send telegrams was not available, the cases were assigned to field workers to bring in the contacts. When the contact reported in response to the telegram, or as the result of field activity, he was interviewed by the Director of the Epidemiology Section or by a designated staff member.

Only persons meeting the following criteria were included in the study:

1. There was no syphilis diagnosis previously reported to the health department, and the contact did not admit ever having had such a diagnosis.
2. No penicillin had been given for any reason subsequent to the exposure date.
3. Exposure date did not exceed 3 months.

Those meeting these criteria were divided into control and treatment groups. In order to avoid any "discretionary" selection and also in order to give the laboratory time to do immediate serologic examinations, a time schedule was used in the assignment of the cases to these groups. From 9:00 a.m. to 2:30 p.m. the first of each three contacts reporting were designated as control cases, the next two as treatment cases. From 2:30 on the contacts were placed in the control group. A check was made once a week by the Epidemiology Section to determine the number of cases in each group. If either group was out of balance all contacts reporting between 9:00 a.m. and 2:30 p.m. were placed in the smaller group until a balance was secured.

After a contact was interviewed a complete diagnostic examination was made. Blood specimens from those persons with no history or clinical evidence of syphilis were sent immediately to the laboratory. After the existence of syphilis had been ruled out by serologic examinations, 600,000 units of penicillin in peanut oil and beeswax were administered to those in the treatment group. If the contact in either group was found to have syphilis at the time of the first examination the case was dropped from the study.

Contacts in both groups were instructed by the clinic epidemiologist to return for observation every 2 weeks for 3 months and once a month for the next 3 months, for a total of 6 months from the date of the first examination. Each clinic visit included a blood serology and a thorough examination for evidence of syphilis.

Any contact in the control group who had gonorrhea upon his

first, or subsequent visits, was treated with sulfathiazole. If he was in the treatment group and had gonorrhea at the time of his first visit, the penicillin eliminated any evidence of gonorrhea. If he had gonorrhea upon subsequent visits, he was treated with sulfathiazole.

Of the 1,069 contacts who reported, 927 cases were excluded from the study mainly for the following reasons (table 1):

1. Penicillin had been given after the date of exposure.
2. There had been previous treatment for syphilis.
3. The exposure date was over 3 months old.
4. There were positive findings on the first examination.

The remainder, or 142 cases, were accepted for the study. There were 77 cases in the treatment group, and 65 in the control group.

It is very significant in relation to the success of this study that

Table 1.—*Contacts to primary and secondary syphilis cases (August 25, 1947 to August 24, 1948), by study group or reason for deletion from study, and disposition of each case*

	Disposition							
	Total	Not infected	Placed under treatment	Already under treatment	Cannot locate	Moved out of jurisdiction	Other	Case still open
Total cases	1,069	372	300	95	177	82	39	4
Total cases accepted in study	142	105	18	.....	.....	10	7	2
1. Control group	65	39	15	.....	.....	5	4	2
2. Treatment group	77	66	3	.....	.....	5	3	.....
Total cases not accepted in study	927	267	282	95	177	72	32	2
Reason for deletion:								
1. Penicillin for GC since exposure	26	17	7	.....	.....	1	1	.....
2. Penicillin for other reason since exposure	7	5	2	.....	.....	.....	.....	.....
3. Previous treatment for syphilis	136	20	64	45	.....	.....	7	.....
4. Wished to transfer to private physician	34	23	10	.....	.....	.....	1	.....
5. Already under observation or treatment for syphilis	117	23	54	39	.....	.....	1	.....
6. Exposure date over 3 months	95	75	13	4	.....	1	1	1
7. Miscellaneous	86	40	29	3	.....	9	5	.....
8. Positive serology or symptoms on first examination	74	8	62	.....	.....	1	3	.....
9. Reported diagnosis in error	14	9	.....	.....	.....	2	3	.....
10. Failed to respond to telegram; returned by worker without interview for study	105	47	41	4	.....	2	10	1
11. Unable to locate or found to live out of jurisdiction	233	.....	.....	.....	177	56	.....	.....

a median of 6 days elapsed between the date the informant was interviewed and the date the contact reported and was examined.

Results

Of the 142 cases accepted in the study, 71 were males, 71 females, 13 were white and 129 colored, and the median age of all

Table 2.—*Contacts to primary and secondary syphilis cases (August 25, 1947, to August 24, 1948), total cases by age, race and sex*

	Total	Under 20	20–29	30–39	40–49	50 and over	Unknown
Total cases	[1] 1,069	130	657	168	45	10	[1] 59
Male	570	25	354	113	32	10	36
Female	492	105	303	55	13	.....	16
White and unknown	[1] 131	8	52	27	9	2	[1] 33
Male	66	1	24	18	6	2	15
Female	58	7	28	9	3	.....	11
Negro and other	938	122	605	141	36	8	26
Male	504	24	330	95	26	8	21
Female	434	98	275	46	10	.....	5
Total cases accepted in study	142	17	94	24	6	1	.....
Male	71	3	50	14	3	1	.....
Female	71	14	44	10	3	.....	.....
White and unknown	13	1	6	4	2	.....	.....
Male	7	.....	4	2	1	.....	.....
Female	6	1	2	2	1	.....	.....
Negro and other	129	16	88	20	4	1	.....
Male	64	3	46	12	2	1	.....
Female	65	13	42	8	2	.....	.....
Total cases deleted from study	[1] 927	113	563	144	39	9	[1] 59
Male	499	22	304	99	29	9	36
Female	421	91	259	45	10	.....	16
White and unknown	[1] 118	7	46	23	7	2	[1] 33
Male	59	1	20	16	5	2	15
Female	52	6	26	7	2	.....	11
Negro and other	809	106	517	121	32	7	26
Male	440	21	284	83	24	7	21
Female	369	85	233	38	8	.....	5

[1] Seven cases with unknown sex included.

cases examined was 26.2 years. The median age of the male cases was 27.4, of the female cases, 24.7, of the whites and races unknown, 32.6, and of Negroes and others, 25.8. If we compare those accepted in the study with the total number of contacts of primary and secondary syphilis for the same period, we find no significant difference in age, sex or color (table 2).

Of the control group of 65 cases, 21 were contacts of primary syphilis and 44 were contacts of secondary syphilis. Of the 77 cases in the treatment group, 29 were contacts of primary syphilis and 48 of secondary syphilis. In other words, almost twice as many cases were exposed to secondary syphilis as to primary syphilis (table 3).

Table 3.—*Contacts to primary and secondary syphilis cases (August 25, 1947, to August 24, 1948), by study group and type of contact*

	Total	Contact to—	
		Primary syphilis	Secondary syphilis
Total cases	[1] 1,069	296	773
Total cases accepted in study	142	50	92
Control group	65	21	44
Treatment group	77	29	48
Total cases not accepted in study	[1] 927	246	681

[1] Includes 14 cases diagnosed in error.

Of the 18 patients who developed syphilis (15 from the control group and 3 from the treatment group), all 3 in the treatment group developed primary syphilis, 5 in the control group developed primary syphilis, 9 were diagnosed as secondary syphilis and 1 as early latent. (Table 4.) The early latent case never showed signs or symptoms of primary or secondary syphilis.

In both the control and treatment groups, we may assume that there were possible reexposures. Two of the three failures in the treatment group admitted reexposure. In the third case, no reexposure was admitted within the possible incubation period. The control group was not similarly reinvestigated for reexposures.

From tables 1 and 4, we find that a total of 1,069 contacts of primary and secondary syphilis were observed over a period of 1 year, of whom 233 could not be located or had moved out of jurisdiction, leaving 836 contacts who were seen at least once.

Table 4.—*Contacts to primary and secondary syphilis cases (August 25, 1947, to August 24, 1948), by study group or reason for deletion from study, and diagnosis of infected cases*

	Placed under treatment						Already under treatment					
	Total	Primary	Secondary	Early latent	Other late	Congenital	Total	Primary	Secondary	Early latent	Other late	Congenital
Total cases	300	45	94	100	57	4	95	16	38	24	14	3
Total cases accepted in study	18	8	9	1								
1. Control group	15	5	9	1								
2. Treatment group	3	3										
Total cases not accepted in study	282	37	85	99	57	4	95	16	38	24	14	3
Reasons for deletion:												
1. Penicillin for GC exposure	7	5	1		1							
2. Penicillin for other reason since exposure	2		1	1								
3. Previous treatment for syphilis	64	5	13	27	17	2	45	10	17	15	3	
4. Wished to transfer to private physician	10	1	3		6							
5. Already under observation or treatment for syphilis	54	7	21	10	16		39	5	18	8	7	1
6. Exposure date over 3 months	13		2	10		1	4	1	2			1
7. Miscellaneous	29	6	12	7	4		3				2	1
8. Positive serology or symptoms on first examination	62	7	22	29	4							
9. Reported diagnosis in error												
10. Failed to respond to telegrams returned by worker without interview for study	41	6	10	15	9	1	4		1	1	2	

Three hundred and ninety-five of these contacts were either placed under treatment or were found already under treatment. Therefore, 47.2 percent of the total group examined for syphilis were found to be infected.

Fifteen patients in the control group developed syphilis, 3 in the treatment group, giving a cumulative infection rate of 25.45 percent in the control group and 4.35 percent in the treatment group (table 5). This difference is statistically significant.

In the control group the median number of days which elapsed between the date of the last exposure to the informant and the date the first symptoms of syphilis were observed by the examining

Table 5.—*Contacts to primary and secondary syphilis cases (August 25, 1947, to August 24, 1948), cumulative infection rate of contacts accepted in study*

Period (in days)	Control group	Treatment group
1–29		
30–59	4.62	
60–89	19.95	
90–119	23.59	2.90
120–149	25.45	2.90
150–179	25.45	4.35
180	25.45	4.35

physician was 66. The approximate period in the treatment group was almost twice as long. Those in the control group who developed syphilis showed evidence long before those in the treatment group. The same applies to the number of days between the date of the last exposure to the informant and the date of the last negative blood test before symptoms of syphilis appeared in the contacts. Here the median of the control group was 46 days, and almost twice that time in the treatment group.

Thirty-eight days after the last day of exposure, the first case in the control group had positive findings upon examination. In no case did the positive findings develop later than 146 days after exposure. The comparable time in the treatment group (from 108 to 161 days) was on the average almost twice as long. This delay in the development of positive findings in the treatment group may be accounted for by the penicillin.

It is of interest to compare the failure rate of the treatment group found by Alexander and Schoch and that found in our study. The failure rate in this study is not significantly different from that reported by Alexander and Schoch, though there is quite a difference in the amount of treatment given in the two studies.

Conclusions

If the exposure date is not in excess of 3 months prior to the examination of a contact of infectious syphilis, it would appear that 600,000 units of penicillin in oil and beeswax are sufficient to prevent syphilis in the large majority of such contacts. Therefore, every contact of primary and secondary syphilis should be treated prophylactically, if found negative upon first examination, and should be given physical examinations and serologic examinations monthly for 6 months.

References

1. Eagle, Harry; Magnuson, H. J.; Fleischman, Ralph: Relation of the size of the inoculum and the age of the infection to the curative dose of penicillin in experimental syphilis, with particular reference to the feasibility of its prophylactic use. J. Exper. Med., 85: 423–440.
2. Alexander, L. J.; Schoch, A. G.: Results of treatment of over one hundred contacts of patients with early syphilis with a "one-day abortive cure." Recent Advances in the Study of Venereal Diseases—1948. P. 263. Venereal Disease Education Institute, Raleigh, N. C.

Abortive Treatment of Syphilis [1]

Results Obtained in the Incubation, Primary, and Secondary Stages of Syphilis

Lee J. Alexander, Arthur G. Schoch, and Walter B. Mantooth

This paper is a report on 2½ years of experience with the treatment during the *incubation stage* of persons who were exposed to darkfield positive *primary* and *secondary syphilis.* It is also a preliminary report on the use of abortive treatment in primary and secondary syphilis.

One year ago we reported on the results of treatment during the incubation stage of 115 persons who were exposed to infectious syphilis. This treatment consisted of giving 900,000 units of calcium penicillin in oil and beeswax in one buttock, 3 cc. of bismuth ethylcamphorate (120 mg. of elemental bismuth) in the other buttock, and 0.05 to 0.06 gm. of arsenoxide intravenously at one clinic visit. The treatment was termed abortive treatment of syphilis. During the ensuing year we have treated 128 additional persons, 95 of whom were treated with penicillin in oil and beeswax (900,000 units) and bismuth ethylcamphorate (3 cc.) alone (the mapharsen having been omitted from the treatment formula). This modification has now replaced our original abortive treatment formula.

Table 1 shows the results of the follow-up observations at each monthly period. Thirteen persons who received the abortive treatment subsequently developed early syphilis; one, 2 months; one, 3 months; three, 4 months; two, 7 months; one, 10 months; one, 11 months; two, 14 months; and two, 23 months after treatment. Ten of these patients are persons who received penicillin, bismuth, and arsenoxide. Three received penicillin and bismuth alone: One of the three showed evidence of early syphilis 3 months after abortive treatment; the other 2 showed evidence 7 months after abortive treatment.

[1] From the Dallas Syphilis and Venereal Disease Clinic and The Southwestern Medical Foundation.

Table 1.—*Abortive treatment of "uninfected" contacts of patients with infectious syphilis*

[Treated group—results of follow-up]

	Number treated	Periods of observation (months)													
		1	2	3	4	5	6	7	8	9	10	11	12	13–18	18+
Patients	243	228	213	205	190	176	165	157	147	134	124	115	107	85	20
Reinfections			1	[1]1	3			[1]2			1	1		2	2

[1] These are patients who were treated with the modified abortive treatment.

Table 2 shows the data on the 13 persons who developed early syphilis after they had received abortive treatment. These patients were re-treated with abortive treatment. Column 1 shows the patients' identification and shows the dates on which abortive treatment was given. Column 2 shows the clinical diagnosis, proved by darkfield examination and serologic tests, and the dates on which these persons were found to have early syphilis. Three had seronegative primary, 7 had seropositive primary, and 3 had secondary syphilis. One patient (47-744 F.M.M.) was found to have seropositive primary syphilis 4 months after receiving abortive treatment. This patient was re-treated with abortive treatment, the serologic tests became negative, and 7 months after this episode was found to have secondary syphilis. Abortive treatment was given for this infection also, and in 5 months the serologic tests became negative and were still negative 7 months later (12 months after treatment for the second infection). Column 3 shows the results of the epidemiologic investigations in these cases. In most instances the evidence strongly indicates that these persons were reinfected subsequently to receiving abortive treatment for incubation stage syphilis. Certainly they were given the opportunity to be. Eight of the patients definitely were re-exposed to infectious syphilis; 3 named pick-ups which we were unable to locate because of insufficient information; 1 refused to give any information at all, but 3 months before acquiring early syphilis (or 11 months after abortive treatment) was treated by us for gonorrhea; 1 (48-1317 S.L.F.) named her husband as contact, but to date we have been unable to investigate him. Column 4 shows the results of re-treatment with abortive treatment of these 13 patients who acquired infectious syphilis. The results thus far are excellent. Eleven have become clinically and serologically negative; 2 just recently have been treated (6 weeks' observation) and their serologic titers are definitely decreased.

Table 2.—*Patients who developed infectious syphilis following abortive treatment*

Patient and date of abortive treatment	Reinfection, diagnosis and date	Epidemiology		Results following re-treatment with abortive treatment
		Source	Results of investigation	
46–3006 E.L.D. 12–16–46	Seronegative primary 11–20–47	46–733 E.M.D.	Secondary 11–26–47 ???	Negative 1 month later. Lost.
47–418 De H. 3–4–47	Seropositive primary 5–27–47	Pick-up 47–1091 42–2472	??? Negative Negative	Became negative. Still negative 16 months later.
47–744 F.M.M. 4–11–47	Seropositive primary 8–14–47 Secondary 3–22–48	47–1671 47–1671	Secondary 8–14–47 Secondary 3–22–48	Became negative. Remained negative until 3–22–48. Became negative 5 months later. Still negative 3–20–49.
47–665 S.E. 4–8–47	Seropositive primary 8–26–47	Pick-up	???	Negative in 2 months. Still negative 10 months later 3–16–49.
46–2752 L.B. 11–20–46	Secondary 1–20–48	???	??? G.C. Oct. 1947 200,000 U. penicillin	Negative 5 months later. Still negative 11–4–48.
47–530 E.A. 3–17–47	Seropositive primary 7–22–47	47–1702 47–1704 47–1739 47–1146	Primary 8–20–47 Negative Secondary 8–25–47 2 months duration Secondary 6–11–47	Negative 10 months later.
47–1862 R.H. 9–11–47	Seropositive primary 7–14–48	47–1871	Secondary 7–16–48	Negative 5 months later. Still negative at 7 months 2–15–49.
47–2376 R.L.B. 11–21–46	Seronegative primary 10–23–48	48–1923 48–2005	Secondary 10–13–48 Negative 10–27–48	Still negative 5 months later. 3–16–49.
47–2004 K.M.J. 10–1–47	Seropositive primary 12–28–48	48–2366 3 unknown	Secondary 12–27–48 2 months duration	Negative 3 months later.
45–1009 G.E. 11–18–46	Secondary 10–26–48	48–1998	Secondary 10–26–48	Lost.
48–1252 S.D. 9–8–48	Seronegative primary 12–22–48	47–1089 46–285	Seropositive primary 12–15–48 Early latent	Still negative 3 months later.
48–1317 S.L.F. 7–21–48	Seropositive primary 2–4–49	48–1309	???	Titer reduced from 256 units to 16 units in 6 weeks.
44–273 H.M.W. 7–1–48	Secondary 2–10–49	R.L. Pick-up C.E. Pick-up	??? ???	Titer reduced one-half in 1 month.

The patient (47-744 F.M.M.) who acquired infectious syphilis twice responded satisfactorily each time to abortive treatment.

Six persons who received abortive treatment were reexposed to infectious syphilis and were re-treated. All were protected a second time. They have been under observation for 14 to 20 months following their second experience.

Of the patients who returned one week after receiving abortive treatment 10.2 percent showed a "provocative effect," that is, a change in the serologic tests from negative at the time of the abortive treatment to doubtful or positive a few days later, this indicating in all probability that early syphilis existed in these individuals but was not detected clinically. None of these patients have subsequently shown evidence of syphilis.

Table 3 shows the outcome of the control group. The group is composed of 161 "uninfected" individuals who were not given abortive treatment. One hundred (62.1 percent) acquired early syphilis in the usual course of time. Sixty-one (37.9 percent) remained negative, or did not acquire syphilis.

Table 3.—*Control group*

Negative and remained negative		Negative and became positive		Total
Number	Percent	Number	Pereent	
61	37.9	100	62.1	161

The control group was analyzed further to see if the incidence of syphilis which resulted from exposure to darkfield positive primary syphilis differed from the incidence which resulted from exposure to darkfield positive secondary syphilis. Table 4 shows these results. There was no significant difference. Approximately 62 percent of the persons exposed to either primary or secondary syphilis acquired the infection.

Table 4.—*Control group. Incidence of syphilis following exposure to primary and secondary syphilis*

	Exposed to primary syphilis		Exposed to secondary syphilis		Total	
	Number	Pereent	Number	Pereent	Number	Percent
Acquired syphilis	32	62.7	68	61.8	100	62.1
Remained negative	19	37.3	42	38.2	61	37.9
Total	51		110		161	

In order to evaluate further the effectiveness of abortive treatment, we treated with the method 197 patients with primary and secondary syphilis, 148 of whom have been observed for 6 to 20 months. We have re-treated 30 of these patients because of "failure": 21 showed evidence of "clinical failure." Approximately 50 percent of the "clinical failures" were reinfections. The remaining 9 failures were in the form of serorelapse and seroresistance, and there was 1 neurorecurrence.

Of 46 patients with primary syphilis who had adequate follow-up, 2 are still seropositive. There has been 1 relapse, and in another patient the diagnosis is pending between relapse and reinfection.

It is premature to attempt to evaluate the group of 102 patients who had secondary syphilis, and one cannot compare the results in this group with the results which were obtained in incubation stage syphilis. It is worthy of note, however, that two patients in this group had type II spinal fluids when treatment was given: both of these fluids are now normal.

Discussion

We have not found it necessary to consider as separate groups the patients who were treated by the original abortive treatment schedule and those who were treated by the modified schedule. The results thus far are as good with the one as with the other. We feel that in the abortive treatment of syphilis mapharsen is probably not necessary; that penicillin and bismuth as used in this study are 100 percent effective in preventing syphilis in persons who have been exposed to infectious syphilis. The "failures" which occur are not true failures: They are reinfections.

We have not treated early infectious syphilis (primary and secondary) with the abortive treatment formula, namely, penicillin in oil and beeswax, bismuth ethylcamphorate, and mapharsen in order to devise a new 1-day method of treatment of syphilis. We did this merely to evaluate its true effectiveness in early syphilis so as to aid in proving that abortive treatment is effective in incubation stage syphilis. The results thus far are surprisingly good. We are not recommending this method of treatment for early syphilis at the present time but it seems to be equally as good as most methods that are being used today.

The Dynamics of Penicillin Action in Relation to Its Use in the Treatment of Syphilis

A Recapitulation of the Experimental Data

Harry Eagle

The experimental data with respect to the spirocheticidal action of penicillin in vitro and its therapeutic action in experimental rabbit syphilis, and the results which have been obtained in the treatment of human infection, all indicate that its action in this disease does not differ qualitatively from that in other bacterial infections. The pharmacologic, bacteriologic, and host factors which modify its action in the acute bacterial infections are operative in syphilitic infection also.

In the first place, the bulk of evidence indicates that the therapeutic action of the drug is largely defined by the total time for which it remains at concentrations lethal to the particular organism. By modifying the schedule of administration, the absolute curative dose of penicillin may be varied to an extraordinary degree. This phenomenon is not peculiar to syphilitic infection, but has been observed in a wide variety of infections involving group A and group B β-hemolytic streptococci, type I and type III pneumococci, and tested in both mice and rabbits. If one uses the serum level as a first approximation of the concentration of penicillin at the focus of infection, one can estimate for how long a time penicillin has been present in concentrations effective against the particular organism. When one makes these calculations, the significant fact emerges that, despite the wide variations in the absolute curative dose on different schedules of penicillin administration, those equi-effective schedules have in common the fact that they provide effective levels for essentially the same total period of time. The total duration of effective levels thus appears to be the primary determinant of therapeutic activity (*1*).

The minimum effective level will, of course, vary according to the bacterial species, and for different strains of the same species. There is reason to believe that the minimum concentration of penicillin necessary to effect cure in a given infection is of the same order of magnitude as that which is bactericidal against the same organism in vitro. *Treponema pallidum* is exquisitely sensitive to penicillin, and, is indeed one of the most sensitive of all the organisms which have yet been studied in this respect. This is indicated by the fact that as little as 7 units of aqueous penicillin per kilogram given often enough to syphilitic rabbits suffices to cure the infection in half the cases. It is more than a coincidence

that this is precisely the dosage of drug required to initiate a Jarisch-Herxheimer reaction in man. Thus, Farmer (*2*) has found that 5 units per kilogram does not cause a Herxheimer in man, while 10 units per kilogram does. By extrapolating the known data with respect to blood levels as a function of dosage, one may estimate that a dosage of 7 units/kg. in rabbits would provide a blood level one-half hour after the injection of approximately 0.005 units/cc. In man, the corresponding value would be on the order of 0.01 units/cc. One may take the sensitivity of *T. pallidum* to penicillin in vitro to be of approximately this order of magnitude, comparable to that of the most sensitive bacteria we have so far encountered.

Are larger concentrations of penicillin more effective than lower concentrations? Within narrow limits, with every organism so far studied, and presumably with *T. pallidum* as well, the rate at which bacteria are killed by penicillin does increase with its concentration. The range between the minimal bactericidal concentration, and that which is maximally effective is, however, quite narrow. One quickly attains concentrations maximally effective; and the rate of bactericidal action is not further increased even by a 10,000-fold increase of the concentration in the drug. Large dosages of penicillin have, however, two obvious advantages over small doses. By providing a higher concentration in the circulating blood, a head of pressure is applied which promotes the rapid penetration of penicillin into tissues. As a result, even tissues which are only slowly equilibrated with the blood plasma, or tissues in which penicillin is perhaps rapidly inactivated, may receive an adequate quota of the drug; while with quite small doses, penicillin may be present in barely adequate concentrations in plasma, but may not attain an adequate concentration at the focus of infection itself. The second advantage of the larger dose is that it provides these effective levels for a longer period of time, and reduces the number of injections necessary.

How long should penicillin be kept at the effective concentration? It is apparent that, everything else being equal, an infection with an organism of which 99.9 percent can be killed by penicillin in less than 2 hours can be cured more readily than one for which 20 hours are required to achieve the same result. Gonorrhea and syphilis afford one of the most striking examples of contrast in this respect. Gonorrhea can be cured by dosages so small that effective levels of penicillin in the tissues are provided for only 2 to 3 hours; while syphilitic infections require the provision of effective levels for a minimum of 30 hours in rabbits, and in man that time period is considerably longer. At least in part, the

difference between gonorrhea and syphilis lies in the rate at which the two organisms can be killed. *T. pallidum* is thus a paradox. In terms of concentrations of penicillin necessary to kill, it is one of the most sensitive organisms yet studied. In terms of rates of death, however, it is one of the most resistant.

The relative susceptibility of bacteria to penicillin is only part of the story. Another factor is the number of organisms to be killed. It is apparent that the more organisms in the body, the longer time will be required to kill them all and to effect cure. Corollary to this is the age of the infection. With every experimental infection so far studied, including syphilitic infection in rabbits, in the early stages of the infection, when the bacteria are rapidly multiplying, the older the infection the more penicillin is required for cure.

The practical significance of these observations is clear. The earlier treatment is instituted, the shorter will be the time required for penicillin to effect cure. Perhaps even more important, however, are certain implications with respect to the prophylactic use of penicillin. The amount of penicillin required to abort an infection soon after exposure should be and is a minute fraction of the amount necessary to cure the established infection (*3*). Thus, in collaboration with a group of Navy physicians, we have been able to show that gonorrhea can be effectively prevented by a single tablet of penicillin taken by mouth within a few hours after exposure (*4, 5*) ; and some studies in the abortive treatment of syphilis in contacts of early cases of syphilis will be here reported by Eisenberg and Plotke (*6*).

Is it necessary that the effective concentrations of penicillin be continuously maintained, or may the injections be given so infrequently that in the interval between injections the penicillin falls to levels which are wholly ineffective? A basic observation on this point was made by Parker and Marsh in 1945 (*7*), who found that staphylococci which had been briefly exposed to penicillin did not immediately resume multiplication when the penicillin is removed. Instead, there followed a variable period during which the bacteria failed to multiply and were presumably recovering from the toxic effects of the drug. We have found this to be a general phenomenon, observed with every bacterial species so far studied. Further, during this period of recovery, the bacteria remain susceptible to the defense mechanisms of the host (*8*). It follows that the therapeutic action of penicillin outlasts for at least a few hours the time for which penicillin remains in the tissues. At least to this extent, blood levels can be discontinuous without adversely affecting the result of treatment.

Summary

In summary, the experimental data in syphilis and other infections indicate that there should be but little difference in the therapeutic efficacy of aqueous penicillin whether it is given every 1, 2, 3, 6, or indeed 12 or 24 hours provided only that the effective levels are provided for a sufficient aggregate period of time. At least in early syphilis, there should be little or no difference in therapeutic efficacy between aqueous penicillin, penicillin in oil and beeswax, aqueous procaine penicillin, or procaine penicillin in oil, with or without aluminum monostearate. The sensitivity of the organisms to penicillin is such that any of those dosage forms will provide the drug in sufficient concentration for a varying period of time. The only essential is that the injection be repeated sufficiently often and at such intervals that the effective concentration is provided for a sufficient aggregate time to kill all the organisms, and that the penicillin-free interval between injections be less than the time required for the surviving organisms to recover and resume multiplication.

Conclusions

In closing, I would like to venture some speculations on the vexing problem of treatment failures and why they occur. This problem is not peculiar to syphilitic infection. The same question may be asked in experimental relapsing fever, caused by an organism which, like *T. pallidum*, is susceptible to penicillin, and yet in which massive doses are required to effect cure. Similarly in subacute bacterial endocarditis, no satisfactory explanation has yet been offered for the fact that one may sometimes fail to obtain cure even when the organisms are highly sensitive to penicillin in vitro, or that treatment may have to be continued for many weeks. Any one of the three factors concerned, the drug, the host, and the parasite, may be at fault. Thus, the infection may perhaps localize in areas which are so slowly and incompletely equilibrated with tissue fluids that the concentration of penicillin does not attain effective levels. Perhaps some of the organisms localize in organs in which the penicillin is destroyed even more rapidly than it can penetrate, so that locally the drug is not maintained at effective levels for a sufficient period of time to effect sterilization. Yet another possibility is that first intimated by Biggers (*9*). It has been clearly shown that bacteria are not sensitive to penicillin unless they are actively multiplying. If the organisms happen to lodge in a focus in which, for whatever reason, they find an adverse

environment and are not actively multiplying, such organisms would not be susceptible to penicillin action and might become what Biggers has termed "persisters." This problem of treatment failure offers a fruitful area for experimental study.

References

1. Eagle, H.: The effect of the method of administration on the therapeutic efficacy of penicillin: The importance of both the total duration of effectively bactericidal levels, and the recovery period. (In preparation.)
2. Farmer, T. W.: Jarisch-Herxheimer reaction in early syphilis treated with crystalline penicillin G. J.A.M.A., 138: 480–485, 1948.
3. Eagle, H.; Musselman, A. D.; Fleischman, R.: The effect of the size of the inoculum and the age of the infection on the curative dose of penicillin in experimental infections with streptococcus, pneumococcus and *T. pallidum*. (In preparation.)
4. Eagle, H.; Gude, A. V.; Beckmann, G. E.; Mast, G.; Sapero, J. J.; Shindledecker, J. B.: Prevention of gonorrhea with penicillin tablets. Pub. Health Rep., 63: 1411–1415, 1948.
5. Eagle, H.; Gude, A. V.; Beckmann, G. E.; Mast, G.; Sapero, J. J.; Shindledecker, J. B.: Prevention of gonorrhea with penicillin tablets. J.A.M.A., 140: 940–943, 1949.
6. Plotke, F.; Eisenberg, H.; Burke, A. H.; Laughlin, M. E.: Penicillin in the prophylactic treatment of syphilis. Read at the Symposium on Recent Advances in the Study of Venereal Diseases, April 7-8, 1949, Washington, D. C. (P. 260.)
7. Parker, R. F.; Marsh, H. C.: The action of penicillin on staphylococcus. J. Bact., 51: 181–186, 1946.
8. Eagle, H.; Musselman, A. D.: The slow recovery of bacteria from the toxic effects of penicillin. J. Bact. (In press.)
9. Bigger, J. W.: The bactericidal action of penicillin on staphylococcus pyogenes. Irish J. Med. Sci., 553–568, 585–595, 1944.

Penicillin in Oil with Aluminum Monostearate: Its Effect on Prolonging Blood Concentrations of Penicillin, and a Preliminary Report of Its Use in the Treatment of Syphilis

S. R. Taggart,[1] F. D. Hendricks,[1] V. L. Chandler,[2] Henry Welch,[2] E. Q. King,[2] D. M. Harley,[1] and S. Olansky [1]

The District of Columbia Bureau of Venereal Diseases and the Penicillin Control Division of the Food and Drug Administration conducted a study to determine the number of days various doses of procaine penicillin G in oil containing 2 percent w/v of aluminum monostearate would maintain a measurable blood concentration, and its use in the treatment of early syphilis. The penicillin utilized was from 87 certified lots from 7 manufacturers. A micronized form (i.e., 95 percent of the particles less than 5 microns in diameter) was contained in 35 of the lots tested. This was administered to 65 subjects. A nonmicronized form (particle

[1] Bureau of Venereal Diseases, District of Columbia.

[2] Food and Drug Administration, Federal Security Agency, Washington, D. C.

size unspecified) was contained in 52 lots. This was administered to 85 subjects.

Experimental

In this study, 147 patients from the venereal disease wards were given varying doses of the product (1.2, 1.5, 1.8, 2.4, and 3.0 million units) in one or two intragluteal repository sites. All injections were given between 9:00 and 10:00 a.m. Blood samples were withdrawn for assay every 24 hours for 10 to 20 days following injection. All assays were performed on the same day the blood was withdrawn. Blood penicillin concentrations were determined by the *B. subtilis* method (*1*) and control (*2*) the minimum measurable concentration by this serial dilution method is 0.03 units per milliliter of serum.

Figure 1 shows the percentage of patients with measurable serum concentrations charted against time in days following injection of the micronized and nonmicronized product. In general the micronized form tended to persist in the blood for a longer time than did the nonmicronized product.

The succeeding charts are regression lines calculated by the least squares of the average blood concentration with time in days.

Figure 2 shows the regression lines computed for different dosage levels, 2.4 and 1.8 million units in one and two depot sites of the micronized and nonmicronized product. Consistency is not shown in initial blood serum levels but in general the micronized product maintained somewhat longer concentrations than did the nonmicronized preparations.

Figure 3 shows a comparison of the micronized product using one deposit with varying doses. Here it will be noted that the average sera concentrations for 2.4 and 1.8 million units are very similar. The concentration for 1.2 million units, while initially approximately one half that for 2.4 and 1.8 million units, tends to be maintained for nearly the same length of time.

Figure 4 shows the regression lines computed for doses of 2.4 million units of the micronized product given in one and two deposits. As would be expected from their respective surface areas (which when maximized could not vary by more than approximately 25 percent) the two lines are not far separated.

Comment

It was noted that frequently patients in this study failed to show measurable blood penicillin concentrations on one or more suc-

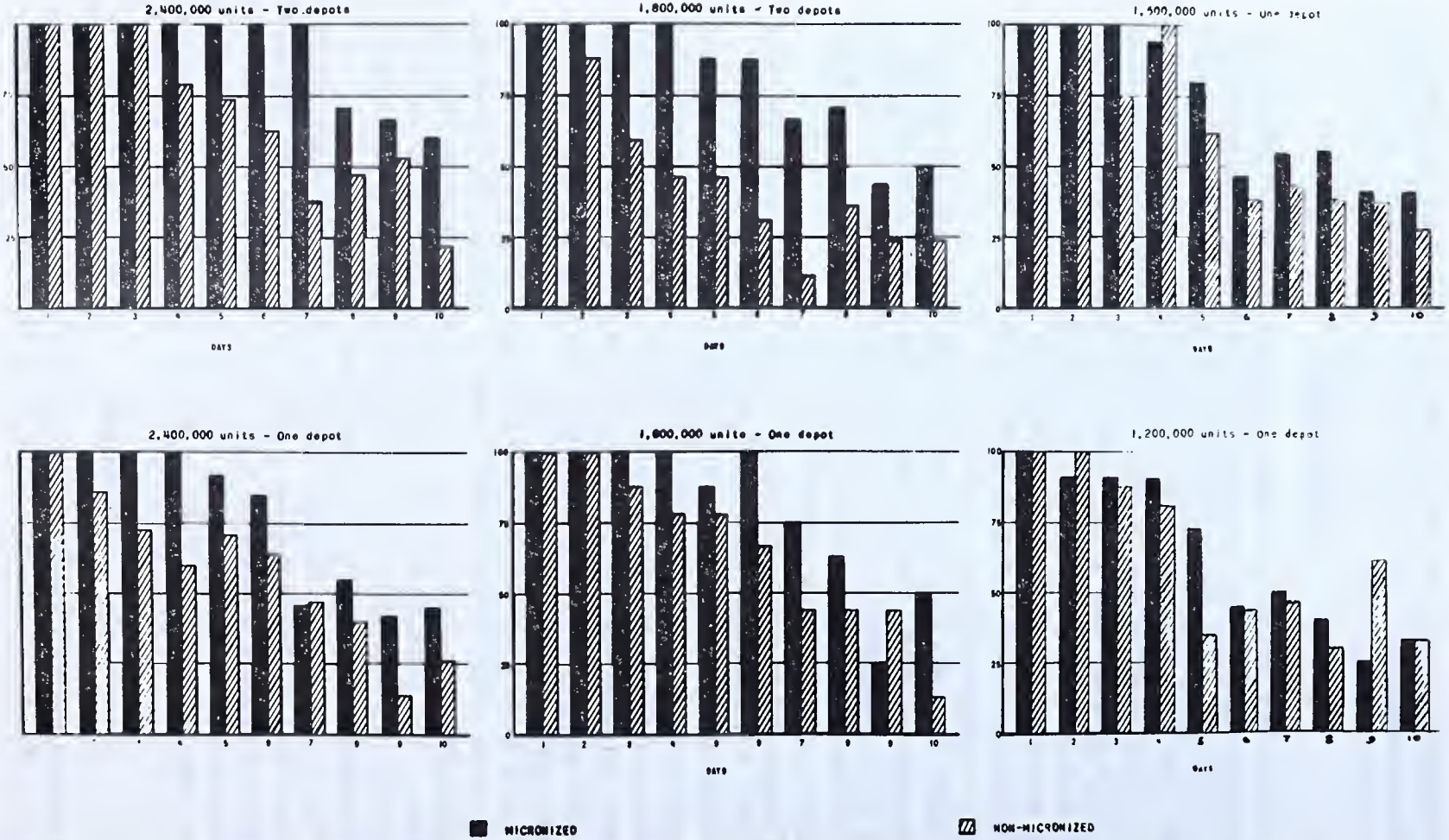


FIGURE 1.—Percentage of subjects with blood concentration of penicillin following injection of micronized and nonmicronized penicillin in oil with 2 percent w/v aluminum monostearate.

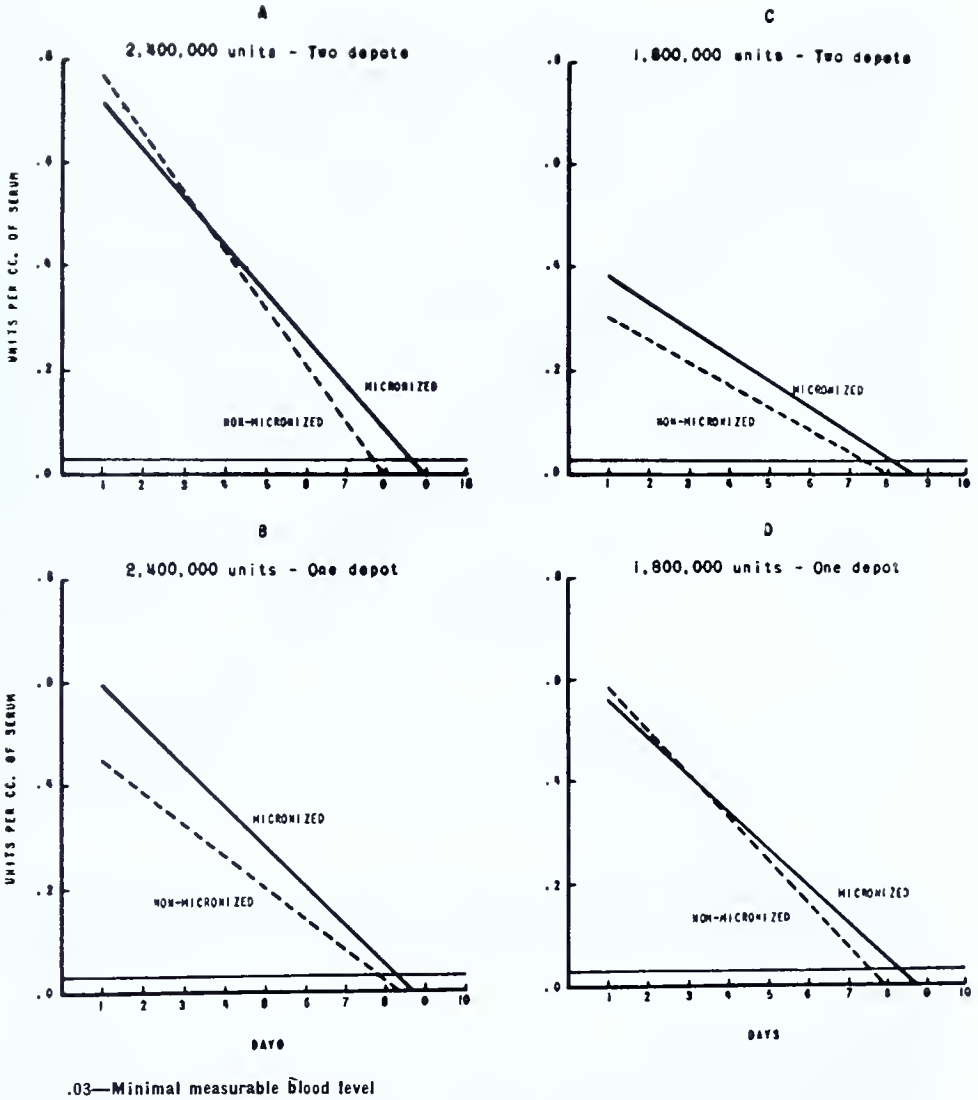
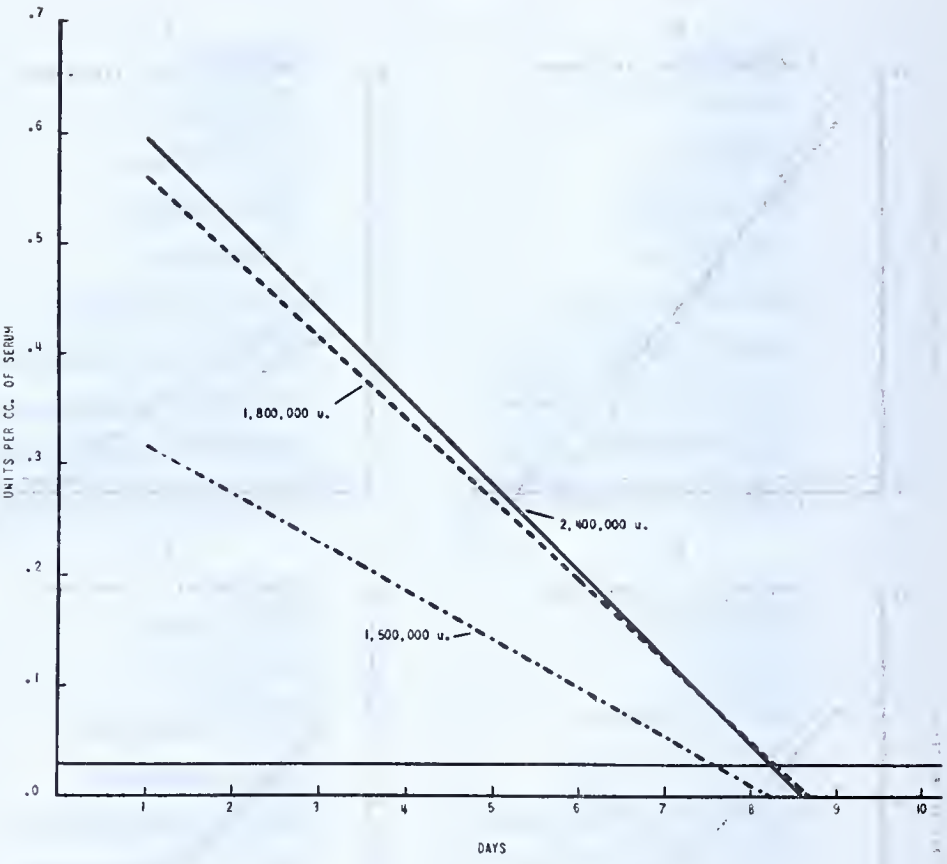


FIGURE 2.—Average blood concentration of penicillin following the injection of micronized and nonmicronized procaine penicillin in oil with 2 percent w/v aluminum monostearate.

cessive days, followed by measurable concentrations on succeeding days.

Serums from 32 patients were examined until they no longer showed measurable concentrations. Duration of measurable blood concentration varied from 11 to 20 days.

Jarish-Herxheimer reactions were noted in 12 patients of this group of 147 subjects. These reactions were mostly febrile in character. Possible sensitization phenomena were noted in two. The first developed an eczematoid type of dermatitis of the neck, ears, back and shoulders 12 days after treatment, while the second had a non-pitting edema of the lower extremities 9 days after treatment and moderate fever from the fifth to the tenth day.



.03—Minimal measurable blood level

FIGURE 3.—Average blood concentration of penicillin following the injection (one depot) of micronized penicillin in oil with 2 percent w/v aluminum monostearate, by amount of penicillin.

Amounts of the preparation up to 10 cubic centimeters gave but little pain or discomfort when administered either into the gluteal or the deltoid muscle.

The District of Columbia Bureau of Venereal Disease has made a previous study (unpublished) of patients with early syphilis treated with penicillin in oil and beeswax and with procaine penicillin in oil, 0.6 million units given in five daily injections, which demonstrated a satisfactory cure rate. Our previous experience suggested that treatment with a penicillin product maintaining effective blood levels for 5 days would give comparable results. To examine this hypothesis, ninety-seven patients with early syphilis were treated with one injection of procaine penicillin in oil and 2 percent aluminum monostearate; 1.2, 1.5, 1.8, 2.4, and 3.0 million units. Twenty-five patients have been followed for 6 months, 41 patients have been followed for 3 months, and 31 patients have been lost from the study.

Table 1 shows the serologic status of cases of primary and secondary syphilis after treatment with one injection of procaine penicillin with 2 percent aluminum monostearate by stage of dis-

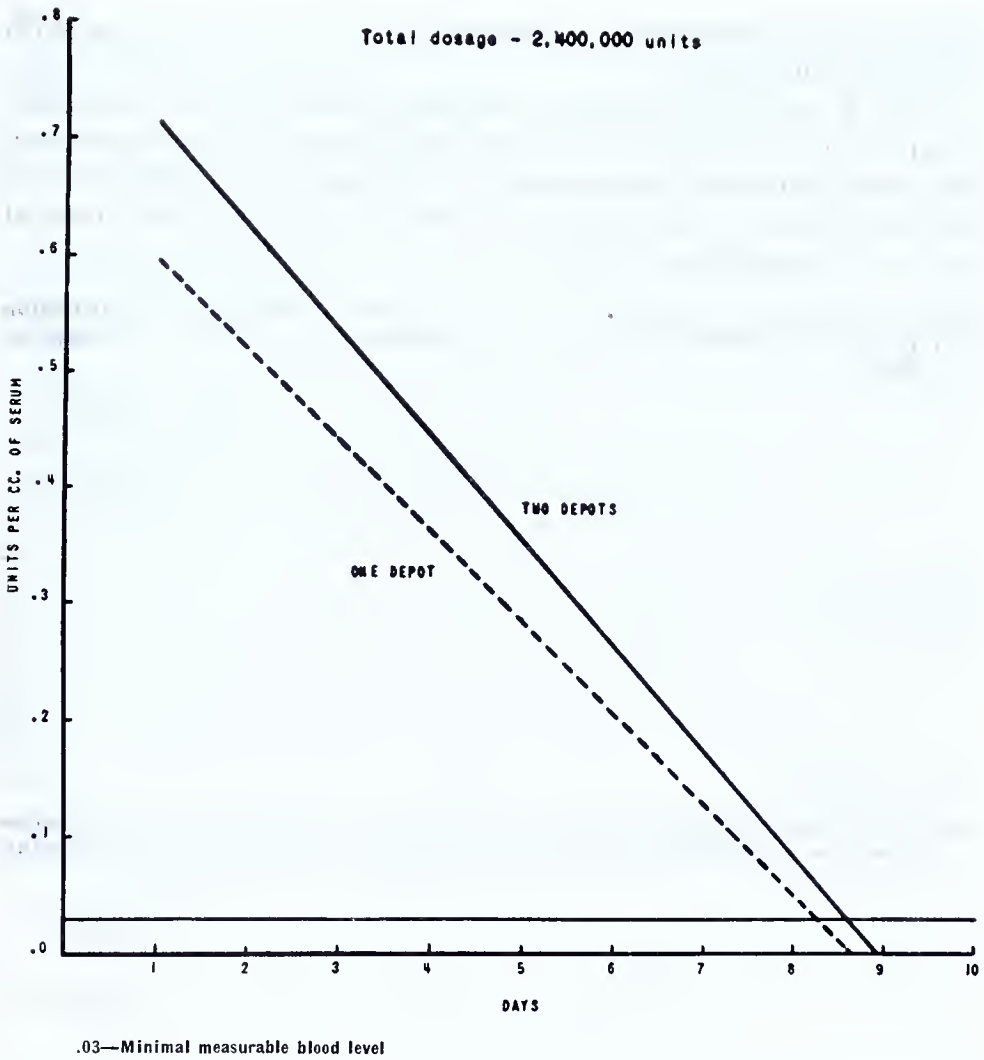


FIGURE 4.—Average blood concentration of penicillin following the injection of micronized penicillin in oil with 2 percent w/v aluminum monostearate, by one and two depots.

ease. Thirty-one seronegative primary, 25 seropositive primary and 29 secondary syphilis are shown. The first three classifications in the table are of previously untreated syphilis. The fourth classification includes patients previously treated who presented themselves during the present study with another infectious episode. Both primary and secondary syphilis are represented in the 12 patients in this classification. A total of 44 patients have attained seronegativity, 20 patients are still seropositive, 14 patients at 3 months and 6 patients at 6 months. The serologic progress in all of these patients except one is considered satisfactory, that is, showing a downward trend. One patient, however, has shown an increase in the titer of his serologic test at the time of his last examination, from a dilution of 1:2 (8 units) to 1:8 (32 units). Two patients have been re-treated, one with

clinical and epidemiological evidence of reinfection, and one with evident clinical relapse.

Table 2 shows the serologic status of primary and secondary syphilis after one injection of differing amounts of procaine penicillin with aluminum monostearate. No appreciable difference in serologic status can be seen at this time with patients grouped at the two different dose levels.

Table 1.—*Serologic status of primary and secondary syphilis after one injection of procaine penicillin with 2 percent aluminum monostearate, by stage of syphilis*

Stage of syphilis	Number treated	Results at 3 months				Results at 6 months			
		Negative	Positive	Retreated	Total	Negative	Positive	Retreated	Total
Seronegative primary	31	19			19	7		[1] 1	8
Seropositive primary	25	4	1		5	4	1		5
Secondary	29	4	10		14	5	4		9
Probable reinfection	12		3		3	1	1	[2] 1	3
Total	97	27	14		41	17	6	2	25

[1] Probable reinfection.
[2] Clinical relapse.

Table 2.—*Serologic status of primary and secondary syphilis after one injection of procaine penicillin with 2 percent aluminum monostearate, by schedule of treatment*

Amount of treatment	Number treated	Results at 3 months				Results at 6 months			
		Negative	Positive	Retreated	Total	Negative	Positive	Retreated	Total
1,200,000, 1,500,000 and 1,800,000 units	41	18	7		25	12	3	[1] 1	16
2,400,000 and 3,000,000 units	56	9	7		16	5	3	[2] 1	9
Total	97	27	14		41	17	6	2	25

[1] Probable reinfection.
[2] Clinical relapse.

Acknowledgment

We are indebted to Mr. Richard Bowman and Mrs. Eleanor V. Price of the United States Public Health Service for the statistical analysis of this data.

References

1. Randall, W. A.; Price, C. W.; Walsh, H.: The estimation of penicillin in body fluids. Science Volume 101. P. 365, 1945.
2. Chandler, V. L.; Price, C. W.; Randall, W. A.: Control and evaluation of blood serum assays for penicillin. Science, Volume 102. P. 355, 1945.

Experiences with Single and Multiple Treatment Schedules of Early Syphilis with Procaine Penicillin in Oil and Aluminum Monostearate[1]

Evan W. Thomas, Charles R. Rein, and Delmas K. Kitchen

In a previous publication (*1*) we reported the results of assays of human sera for penicillin following the injection of procaine penicillin (fine particle size) suspended in oil and aluminum monostearate.[2] The preparation contained 300,000 units of procaine penicillin per cubic centimeter and, when injected intramuscularly in this amount in 173 patients, a serum concentration of penicillin of above 0.05 units per cubic centimeter was present at the end of the ninety-sixth hour in approximately 90 percent of the subjects. It was hypothesized that such a product would be vastly superior to the older aqueous and repository penicillin products in the treatment of syphilis. The likelihood of curing at least 90 percent of all patients with early syphilis with any penicillin product which would produce constant detectable blood concentrations for a period of 72 to 96 hours was mentioned by Mahoney (*2*). We therefore, devised certain treatment schedules employing single and multiple injections as follows:

Schedule 1.—Single injection of 4 cc.—1.2 million units.

Schedule 2.—Single injection of 8 cc.—2.4 million units.

Schedule 3.—Single injection of 4 cc. once a week for 2 weeks—2.4 million units.

Schedule 4.—Single injection of 4 cc. once a week for 4 weeks—4.8 million units.

Since these were the first patients to be treated on such brief schedules with this particular product, and since we did not wish to risk the possibility of a high failure and relapse incidence, we did not use less than a single injection of 1.2 million units on any schedule.

Simultaneously with the treatment schedules, serums were assayed for the concentration of penicillin produced and maintained by the injections of these varying amounts of this product. Results of these studies, recently published (*3*), report that a single injection of 4 cc. produced an initial peak concentration within the first hour of approximately ½ unit per cubic centimeter and that the serum concentration remains above 0.03 units per cubic

---

[1] From Bellevue Hospital and New York University College of Medicine, New York (Drs. Thomas and Rein), and Bristol Laboratories Inc., New York (Dr. Kitchen).

Read before the Eleventh Annual Session of the American Venereal Disease Association, April 8, 1949, Washington, D. C.

[2] Flo-Cillin "96" was supplied by Bristol Laboratories Inc.

centimeter from 5 to 8 days in a high percentage of patients. A single injection of 8 cc. or two simultaneously administered injections of 4 cc. produced an initial peak concentration of approximately one unit per cc. and the concentration remained above 0.03 units per cubic centimeter for a longer period. (See figure 1.)

In our opinion, these concentrations are far in excess of those necessary for the cure of syphilis. "High peaks of penicillin in the blood are apparently no more effective in destroying the *Treponema pallidum* than very low concentrations" (*4*).

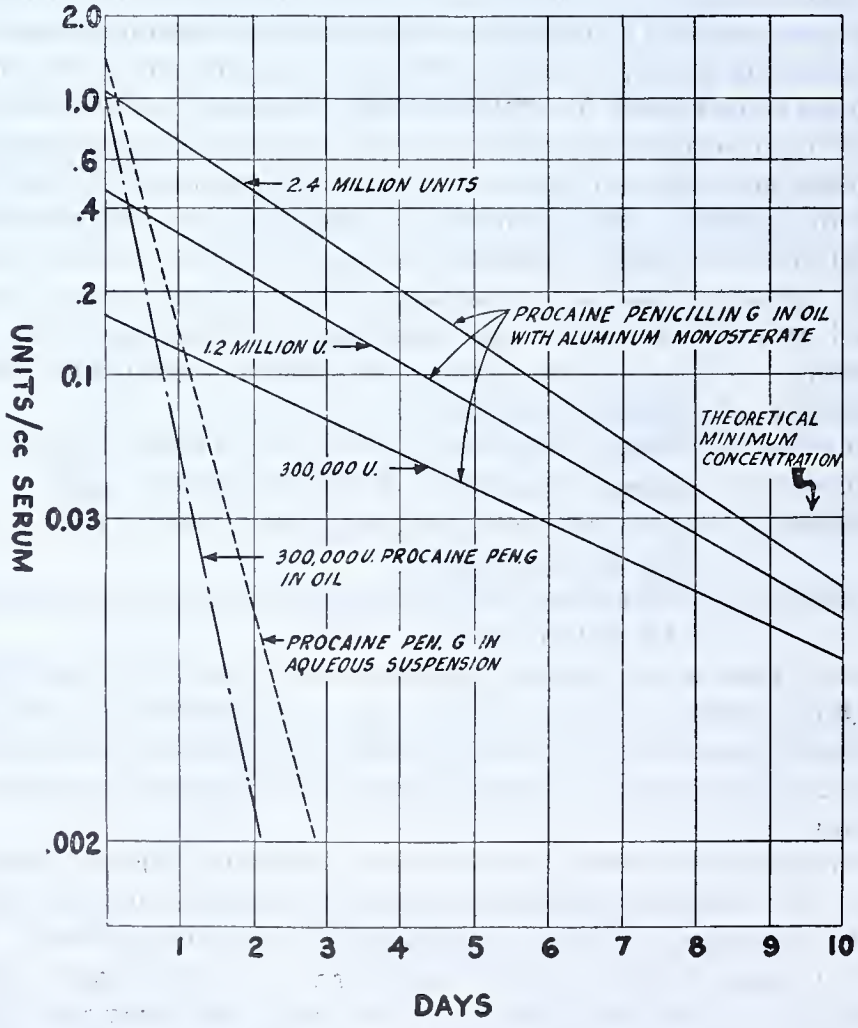


FIGURE 1.

One hundred and sixty patients with primary and secondary syphilis were selected for this study and divided into the four treatment groups mentioned above. A blood specimen was collected from each patient immediately prior to treatment and at

approximately monthly intervals thereafter. Each specimen was subjected to a "battery" of three qualitative and quantitative procedures, including the Kahn standard macroflocculation, Rein-Bossak microflocculation and the Kolmer complement-fixation tests. In the last two procedures cardiolipin-lecithin antigens were employed. In this study, the results reported are limited to those obtained with the Kahn standard and quantitative tests. This is done in order to facilitate comparison of our results with those of other investigators, since the majority of publications pertaining to treatment of early syphilis are based on serologic results obtained with Kahn tests. It should be pointed out, however, that the evaluation of our results would be somewhat different if it had been based on reactions to the other two more sensitive tests. The serologic pattern and degree of serologic improvement evidenced by the reactions to the three tests were similar. In order to evaluate the serologic results obtained in these patients in a 9-month follow-up period, the following arbitrary criteria and definitions were decided on:

Serologic cure.—Seronegativity with the Kahn Standard Test attained and maintained following treatment.

Serologic improvement.—A marked reduction in serologic titer, indicating a satisfactory serologic response but seronegativity not attained.

Serologic fastness.—A failure to show a reduction in serologic titer below the pretreatment level.

Serologic relapse.—An initial reduction in serologic titer followed by a sudden and progressive increase in titer, indicating an unsatisfactory response to penicillin therapy or an asymptomatic reinfection.

It will be noted that 19 patients were lost from observation and an additional 17 patients were followed for less than 3 months. Of the remaining 124 patients there were three classified as failures, one of which was a reinfection. (See table 1.) Although the number of patients treated in each schedule is too few and the period of follow-up too short to allow for any definite conclusions, there appears to be a very satisfactory trend.

No instance of undue irritation or untoward effects was reported by or observed in patients on any of these four schedules. Several patients who received 8 cc. in one depot (schedule 2) reported moderate pain during and for a short time following the injection. The incidence of generalized allergic reactions encountered in our experience to date is about 0.2 percent. This is much less than the incidence of 3 to 5 percent following the injection of calcium or sodium penicillin in peanut oil and wax.

Table 1

Schedules	Serologic cure	Serologic improvement	Failures	Insufficient follow-up	Lost from observation
Single injection of 4 cc.—1.2 million units	5	10	0	1	5
Single injection of 8 cc.—2.4 million units	12	14	[1] 1	0	3
Single injection of 4 cc. once a week for 2 weeks—2.4 million units	13	29	[2] 2	10	8
Single injection of 4 cc. once a week for 4 weeks—4.8 million units	11	27	0	6	3
Total	41	80	3	17	19

[1] Classified as a reinfection.

[2] One patient classified as a serologic resistance and the other as a serologic relapse.

Conclusions

The results obtained with single and multiple treatment schedules of early syphilis with procaine penicillin (fine particle size) in oil and aluminum monostearate are presented. The clinical and serologic response, to date, are excellent. The incidence of local and generalized allergic reactions are extremely low.

References

1. Thomas, E. W.; Lyons, R. H.; Romansky, M. J.; Rein, C. R.; Kitchen, D. K.: Newer repository penicillin products. J.A.M.A., 137: 1517–1519, August 21, 1948.
2. Mahoney, J. F.: Personal communication.
3. Kitchen, D. K.; Thomas, E. W.; Rein, C. R.: Serum concentrations following five treatment schedules with procaine penicillin in oil with aluminum monostearate. J. Invest. Dermat., 12: 111–115, February 1949.
4. Thomas, E. W.: Penicillin treatment of early syphilis. Am. J. Med., 5: 687, November 1948.

Penicillin Therapy in Asymptomatic Neurosyphilis

A Comparison of the Effects of Amorphous Penicillin, Penicillin in Oil and Wax, and Crystalline Penicillin G on the Cerebrospinal Fluid [1]

Fenwick T. Nichols, Jr., and Albert Heyman

Final evaluation of penicillin therapy of neurosyphilis requires many years of observation, but the effects of treatment as reflected by the spinal fluid findings can be determined in a relatively short period of time. The changes in the spinal fluid are considered to be reliable criteria of the efficacy of treatment in the majority of patients with neurosyphilis. These changes are particularly useful in asymptomatic neurosyphilis where spinal fluid abnormalities are the only evidence of central nervous system involvement.

This report presents the spinal fluid changes in 292 patients with early and late asymptomatic neurosyphilis who were treated with various forms and doses of penicillin. All of these patients had strongly positive ("active") spinal fluids before treatment and have been followed for as long as 6 to 48 months after therapy. Treatment failure was determined by persistent elevation of the spinal fluid cell count 6 months or longer following treatment. Only 30 (10.2 percent) of the entire series of patients showed such evidence of treatment failure. Eight (15.6 percent) of the 51 patients treated with the smaller doses, i.e., 2.4 to 3.0 million units, of amorphous penicillin in aqueous solution, developed evidence of failure. The use of 4.0 million units of the same form of penicillin resulted in fewer treatment failures (10.4 percent of 86 cases).

The best spinal fluid response was obtained among the 77 patients treated with 4.8 million units of crystalline penicillin G in aqueous solution. Only 4 (5.2 percent) of these patients are classified as treatment failures. This group of patients has not been followed as long as those treated with amorphous penicillin, and additional failures are expected with further observation. The number of such cases, however, is expected to be very small, since 80 percent of this group of patients have been observed for at least 12 months, and evidence of treatment failure usually develops within this period of time. Nine (11.5 percent) of 78 patients treated with 6 to 9 million units of penicillin in oil and wax have developed spinal fluid evidence of treatment failure. The results obtained with daily injections of 300,000 units of penicillin

[1] From the Clinic for Genitoinfectious Diseases, Grady Memorial Hospital, the Department of Medicine, Emory University School of Medicine, and the Georgia Department of Public Health.
Aided by a grant from the U. S. Public Health Service.

in oil and wax for 20 days appeared to be better than that obtained with triweekly injections of 600,000 units for 5 weeks.

The percentage of treatment failures observed in patients with early neurosyphilis was the same as that in late neurosyphilis. The severity of spinal fluid abnormalities in the patients in this study did not seem to influence the incidence of treatment failures. The number of patients obtaining normal spinal fluids following penicillin therapy was greatest among patients with early neurosyphilis and among those with less severe spinal fluid abnormalities. The blood serologic test for syphilis did not show a rise in titer concomitant with the appearance of spinal fluid evidence of treatment failure.

The spinal fluid response to penicillin (4 to 4.8 million units in aqueous solution) in patients with asymptomatic neurosyphilis was compared with a group of patients with clinical manifestations of neurosyphilis. Six (10.7 percent) of the 56 patients with clinical neurosyphilis showed spinal fluid evidence of treatment failure, while only 10 (7.1 percent) of the 140 patients with asymptomatic neurosyphilis showed similar evidence of therapeutic failure. In both the symptomatic and asymptomatic patients the results obtained with crystalline penicillin G were better than those obtained with amorphous penicillin.

The majority of patients with treatment failure showed evidence of an elevated spinal fluid cell count 6 to 8 months following treatment, but occasionally 12 to 18 months or more were required before definite evidence of treatment failure occurred. The administration of small doses of penicillin for other conditions following the initial therapy for neurosyphilis may delay the appearance of spinal fluid evidence of treatment failure. None of a small group of patients who received combined penicillin and malaria fever therapy showed evidence of treatment failure. Nevertheless, the use of penicillin alone in the initial treatment of patients with asymptomatic neurosyphilis is preferable because of its safety and ease of administration.

Seropositivity in Patients Previously Treated for Syphilis. The Differentiation Between Seroresistance and Treatment Failure

Ira Leo Schamberg [1]

The interpretation of a positive serologic test for syphilis [2] in a patient who has been treated for syphilis in the past is often difficult. The patient presented diagramatically in figure 1 has suffered a relapse or a reinfection, and is in urgent need of further treatment. On the other hand, the case depicted in figure 2 may be showing only the serologic residua of an adequately treated late syphilis. Frequently however, we encounter patients with only the meagre data shown in figure 3, a seropositive patient who several years ago received treatment for syphilis. If no additional information can be obtained, we are in a dilemma as to whether he has followed serologic course A or B in figure 4. Course A indicates that the patient has at the present time untreated early syphilis. (From the immunologic, clinical, epidemiologic and prognostic standpoints, the patient who has relapsed following treatment has untreated syphilis.) Course B suggests late syphilis, which if the treatment has been adequate and the patient is latent, requires no further treatment. The following patients illustrate this problem:

Case 1.—E.S., white female, 42 years of age, single, presented two positive STS in May 1943, and received, from May 1943 to January 1946, 43 injections of bismuth and 40 injections of mapharsen. In February 1945 the spinal fluid was negative, in February 1946 physical examination was negative and the patient was discharged as having had adequate treatment.

In September 1947, 1½ years after her last treatment, she returned with a papulosquamous nonpruritic eruption which was diagnosed as pityriasis rosea. STS was positive, this being the first STS which she had had since May 1943. Two months later the picture was described as an annulomacular generalized erythematous rash with red erosions on the hard palate and red flat papules on the soles. There was no lymph node enlargement and the genitalia showed no lesions. She denied coitus during the past 11 months. It was felt that the patient had either erythema multiforme or secondary syphilis. STS was positive. (It was belatedly learned at this time that in 1943 the patient had presented "chancre right labium majus, generalized maculopapular rash" and had been diagnosed as primary and secondary syphilis.) Two weeks later palmar and plantar ham-red papules were seen, and at this time she was diagnosed as secondary syphilis, reinfection. She received 2.4 million units of aqueous penicillin in 7½ days, and 2 weeks after the completion of treatment, all lesions had completely cleared. STS was positive through the 5 months after treatment, was doubtful the two succeeding months and was negative 8 months after treatment.

---

[1] Philadelphia, Pa.
[2] Hereafter designated as STS.

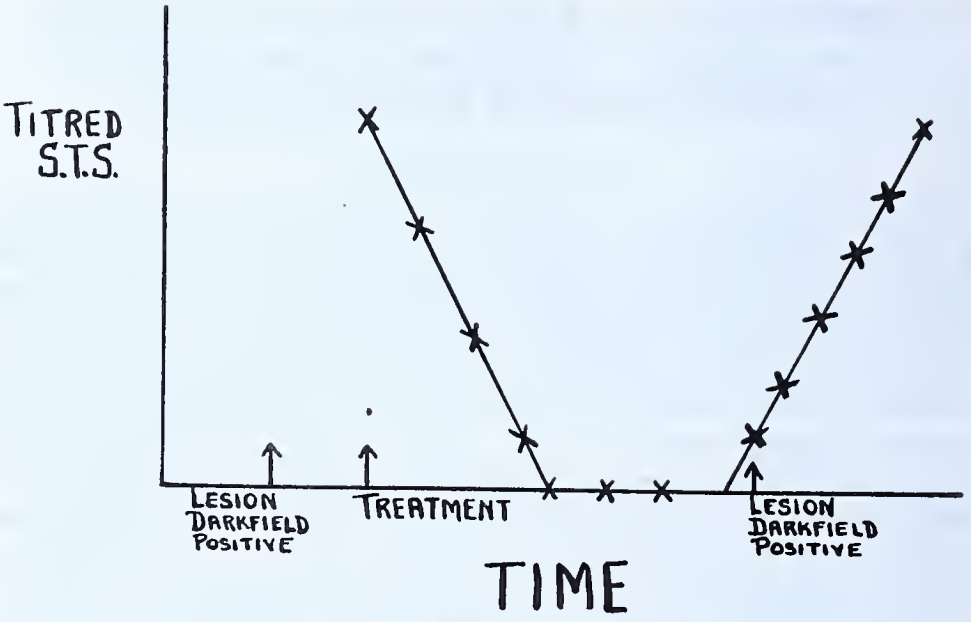


FIGURE 1.

A clear-cut diagnosis of relapse or reinfection was made on the basis of clinical and serologic response to treatment with penicillin.

Case 2.—G.W., colored male, 30 years of age, married, reported to the clinic in March 1948 stating that he wanted a blood test because his wife was under treatment for syphilis by a private doctor. Except for a suppurative

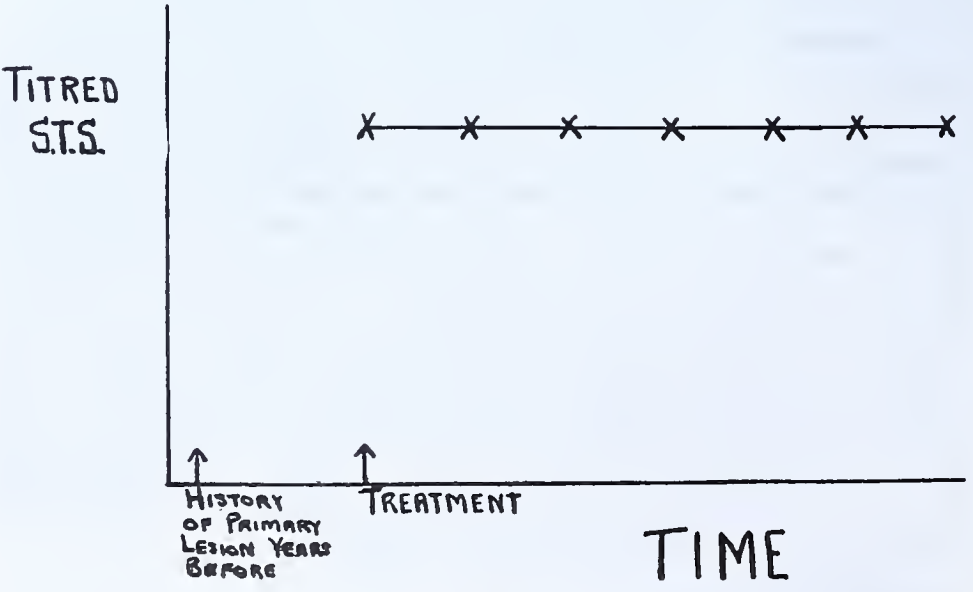


FIGURE 2.

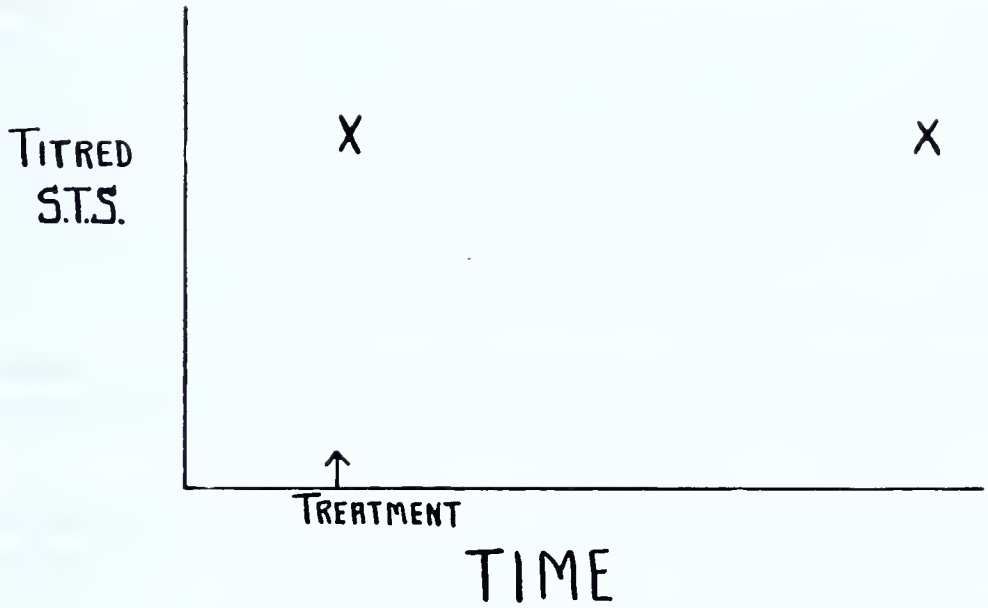


FIGURE 3.

bubo 10 years previously he gave no history of genital lesions. However, as a result of a positive STS on induction into the Army in 1944, he received the semi-intensive 26-week Army treatment with arsenic and bismuth from February to August 1944. Spinal fluid was negative at that time. The only subsequent STS was on separation from the Army in December 1945, the result of which is not known. Physical examination was negative, the STS positive.

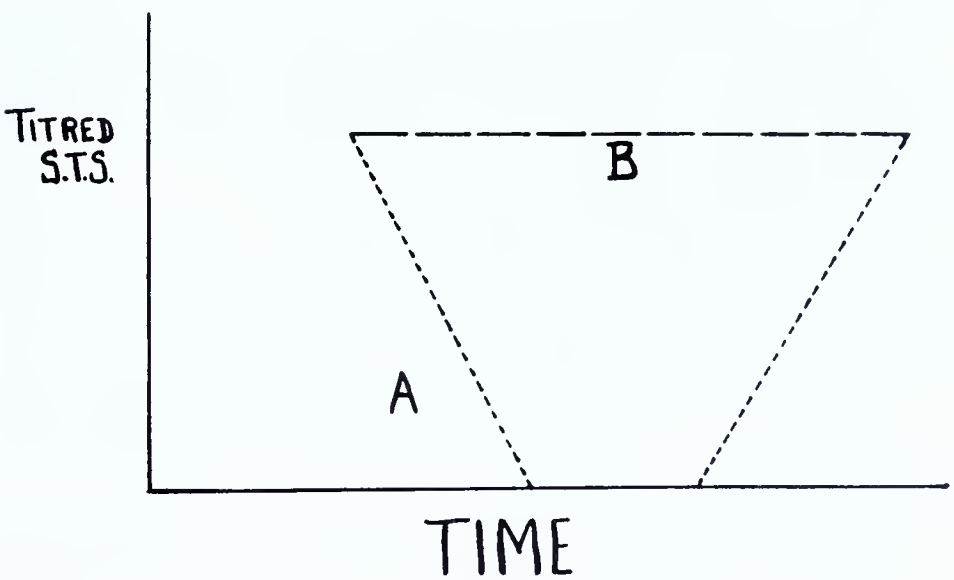


FIGURE 4.

The patient's wife, M.W., was seen a few days subsequently. She stated that she had had a negative STS in January 1946. In January 1947 she went to her private physician for the treatment of a rash on her arms and bumps on her privates. Her STS was positive and she received weekly intravenous treatment regularly for three months, then irregularly, the last treatment having been administered in November 1947. On examination a genital condyloma latum was seen which was darkfield positive for *Treponema pallidum*. Her STS was positive with 256 units. On further questioning the husband belatedly admitted having had a penile sore in April 1947.

He was diagnosed early latent syphilis, reinfection, and treated with penicillin.

Here epidemiologic evidence alone indicated that this patient had relapsed or had been reinfected and was in urgent need of treatment.

Case 3.—J.S., colored male, age 22, single, had a penile sore in August 1947, and received penicillin for primary syphilis. Two months later he came to the clinic with a penile sore of 1 month's duration, which was described as a healing, clean ulcer on the dorsal prepuce and which was darkfield negative for *Treponema pallidum*. Large, hard, nontender inguinal lymph nodes were felt bilaterally. STS was positive, he was diagnosed as primary syphilis, reinfection, and was again treated with penicillin.

He was next seen in February 1948 at which time he stated that he had had a penile sore of 2 weeks' duration 1 month ago, and that he had had headaches and a rash on his arms for the past 3 weeks. Examination revealed no lesions except for moderately enlarged, firm inguinal lymph nodes, and a smooth nonindurated recently healed area on the left inner prepuce. STS was positive with 128 units. On subsequent visits no clinical evidence of early syphilis was found, and qualitative STS remained positive. Finally, the patient refused to return to the clinic stating, "You folks tell me I might infect other people, but every time I come here you just take a blood test." The patient was reported to the City Health Department as potentially infectious and uncooperative.

This patient's plaint was well taken. It was impossible to decide, on the basis of inadequate and irregular follow-up with only qualitative STS, whether or not he had "failed" again. Possibly he was infectious, but the clinician was unwilling to treat a third time without more definite evidence.

Case 4.—C.W., white female, age 23, single, came to the clinic very much perturbed about a positive occupational STS taken 1 week ago. She gave a questionable history of a negative STS 8 years previously. One year ago, when she consulted her physician because of abdominal cramps, she was found to have a positive STS, for which she received adequate penicillin therapy. There was no serologic follow-up after this treatment. She had had a sore throat for 1 week 5 months before coming to the clinic, denied sexual intercourse for the past 17 months except with one man 5 months ago. Physical examination was negative.

Case 5.—R.P., colored female, age 17 years, single, was first seen in November 1947 complaining of a genital sore 3 months ago and a rash for the past 2 weeks. She had never had an STS. On examination, a healed soft scar was seen on the left labium majus and a papulosquamous eruption on

the trunk. The lymph nodes were not enlarged. STS was positive, and she received penicillin treatment for secondary syphilis. The STS remained positive under regular serologic follow-up. In April 1948 she presented a papulosquamous eruption on the trunk of two weeks' duration, which clinically suggested secondary syphilis or pityriasis rosea. The mouth, throat, lymph nodes and genitalia were clear of lesions. STS was still positive. Three weeks later the rash had cleared, leaving only residual pigmentation, and no other lesions were found. She admitted only one sexual partner who was brought to the clinic and found to have no lesions and a negative STS one month after she first noticed the rash. Her STS remained positive through August 1948.

Further study of the contact should have been carried out. If he proved not to have syphilis, it is probable that the patient had pityriasis rosea in April, and not infectious relapse or reinfection.

Unless seroresistance of late syphilis can be differentiated from serorelapse of early syphilis, not only may the patient's future health be endangered by the late manifestations of untreated syphilis, but also the public health is threatened by the free circulation of another individual with untreated infectious syphilis. In addition, long-term evaluation of current methods of treatment of early syphilis is jeopardized.

What shall we think and say 15 years hence, when we find an aortic aneurysm, or paresis, in a patient who received penicillin treatment for early syphilis years before? Many will damn penicillin as ineffective in preventing the late manifestations despite good initial clinical and serologic response. We will, at that late date, certainly be unable to say whether the infection which caused paresis was the same one for which the patient received treatment, or whether he was cured of his first attack of syphilis, and his second attack went untreated and eventuated in paresis. The following measures are of help in deciding the status of the patient:

1. Before treatment, searching anamnestic, clinical, epidemiologic and laboratory study should be made in an effort to establish accurately the stage of the disease. A patient treated for early syphilis who is seropositive years later is strongly suspect of "treatment failure," whereas one first treated late is not.

2. Every effort must be made to achieve regular clinical and serologic follow-up. Serorelapse following treatment is evidence of need for re-treatment, whereas seroresistance is consonant with adequacy of treatment.

3. Quantitative STS are essential and should be performed in a reliable laboratory subject to minimal variation in sensitivity. Qualitative tests, even if carried out at regular intervals, fail to show whether the titer is rising, falling, or remaining at a fixed level.

4. Detailed interim history may reveal a genital lesion since treatment, or a positive or negative STS elsewhere.

5. Epidemiologic study may uncover, as in case 2, exposure to an infectious contact. Conversely, sexual contact over a long period of time with a person found to be nonsyphilitic would speak against "treatment failure."

6. If the patient is re-treated, regular clinical and quantitative serologic study following the second treatment may belatedly tell the story. Seroreversal following re-treatment, as in case 1, demonstrated that the patient had relapsed or had been reinfected after her first treatment.

Summary and Conclusions

1. To safeguard the individual and the public health, and to evaluate the effect of current treatment schemes on the prevention of late syphilitic manifestations, it is essential to differentiate, in the seropositive patient previously treated for syphilis, between relapse and reinfection on the one hand, and seroresistance on the other.

2. Six factors are presented which are of value in this differential diagnosis.

Advanced Banti's Syndrome Associated with Syphilis: Review and Report of Failure of Penicillin Therapy in Two Cases [1]

George W. Hambrick, Jr. and Dudley C. Smith

In 1894, Banti described a clinical picture in which splenomegaly and anemia were the prominent features. Since that time, numerous cases have been reported in the literature under various titles, "Congestive Splenomegaly," "Splenic Anemia," etc. A great deal of interest has been stimulated regarding the etiology. The purpose of this paper is to review the literature regarding the pathogenesis of the condition, to present two cases of Banti's syndrome in which the primary factor in the etiology was probably congenital syphilis, and to report the results of massive penicillin therapy.

[1] From the Department of Syphilology and Dermatology, University of Virginia Hospital, Charlottesville, Va.

Banti (*1*) stated: ". . . that toxic substances develop in the spleen and by invasion of the blood cause anemia. Then, because of their constant passage through the liver, they induce hyperplasia of the connective tissue in that organ with an action similar to that of alcohol absorbed by the intestine. It seems to me that the chronic endophlebitis limited to the splenic vein permits us to conclude that there has been constant passage of poison through this vessel since there is no other cause present to explain the origin of the condition." There has been no confirmation of this idea that a splenic toxin is primary, but several authors, Rives (*2*) and McMichael (*3*), believe that toxin plays a part.

There is clinical and experimental evidence to justify the concept that Banti's syndrome is in most cases the result of mechanical obstruction to the flow of blood within the portal circulation. A persistent increase in the venous pressure of the splenic vein occurs and congestive splenomegaly results.

Rousselot (*4*) and Thompson (*5*) classify their cases in the following manner: (1) Obstructive factor known, (*a*) cirrhosis of the liver, (*b*) thrombosis of the splenic vein, (*c*) cavernous transformation of the splenic vein, (*d*) stenosis of the portal vein; (2) obstructive factor undetermined. Johnston (*6*), using cases of Banti's disease without cirrhosis and cases with cirrhosis, has shown by camera lucida drawings of hepatic arteries and portal veins, that the size of the spleen varied in direct proportion to the degree of capacity loss of the portal vascular system. He also found that the older the patient at the time of onset of his disease the less the splenic enlargement, that the degree of cirrhosis of the liver is not always an index as to the amount of vascular bed loss in the portal system and that the vascular narrowing in the hepatic portal radicals is the important determining factor irrespective of the amount of fibrosis present. Approximately 70 percent of a group of cases (*4*) reported from the Spleen Clinic, Presbyterian Hospital in New York showed a portal obstructive factor at the time of surgical operation. Direct measurement (*7*) of the pressure in the splenic veins of eight cases of Banti's syndrome prior to ligation of the vessel gave readings of 250–500 mm. of water while simultaneous readings in the peripheral veins were 12–140 mm. of water. Three cases of hemolytic jaundice serving as controls showed splenic vein pressures of 105–120 mm.

In normal livers, Herrick (*8*) found a rise of 1 mm. in the portal venous pressure for every 40-mm. rise of arterial pressure in the hepatic artery when this pressure was greater than 100 mm. In contrast, in cirrhotic livers, there was a 1-mm. rise in portal venous pressure for every 6 mm. of hepatic arterial pressure and the

effects were evident when the arterial pressure was greater than 30 mm.

Rousselot and Thompson (*9*), by repeated injections of finely divided particles of silica into the splenic vein in dogs, were able to produce a picture similar to Banti's in which the pressure in the splenic vein was as high as 295 mm. of water. The particles lodging in the portal radicles within the liver produced the obstruction.

Whipple (*10*) believes that the whole picture of Banti's syndrome is explained by mechanical obstruction in the portal system. He divides the cases into two groups, respectively, those with intrahepatic and extrahepatic portal block. In most cases of Banti's syndrome the liver disease is thought to be primary, resulting in a portal hypertension with congestive splenomegaly. In other cases in which the block is extrahepatic, liver disease is not found even after a period of years. At autopsy 79 percent of all cases of cirrhosis of the liver are said to have an associated splenomegaly (*11*). Whipple (*10*) states that in cirrhosis, the amount of portal hypertension present varies as result of variable factors and this serves to explain the absence of splenomegaly in certain cases of cirrhosis.

The inflammatory reaction stimulated by *Spirocheta pallida* in the liver as well as in other tissues, is characterized by perivascular fibrous hyperplasia in the early stages of the infection and this may progress to a fibrotic or cirrhotic state in the later stages of this disease. As indicated previously some individuals with cirrhosis of the liver develop portal hypertension. Syphilis, it can be concluded then, is one of the causes of Banti's syndrome. The syphilitic infection may be either acquired or congenital.

Councilman (*12*) reported the autopsy findings in a case of late syphilis of the liver associated with an enlarged spleen. Osler (*13*) recorded in 1900 the accompaniment of Banti's syndrome with syphilitic cirrhosis of the liver. Korns (*14*), in a review of the records of 170 cases of Banti's syndrome states that in 36 of these a definite diagnosis of syphilis was justified and that there were 30 other cases in which the diagnosis of syphilis was suspected. He concludes that Banti's syndrome is frequently caused by syphilis but in some cases syphilis is not a factor.

Case Reports

Case 1.—M.A.H., colored female, age 8, was admitted to University of Virginia Hospital (#245307) October 1, 1947, with a history of epistaxis, weakness, and abdominal swelling during the past 2 years. The history or clinical findings in other members of the family were not available, except

that the patient was illegitimate and has lived with her aunt since infancy. The child was examined in the Out-patient Department of the Stevens Clinic Hospital (Welch, W. Va.) in February 1946 for "weakness and anemia." At this time her "Hb. was 50%, Rbc. 3,120,000, Wbc. 6,050, and Kolmer-Wassermann test was 4 plus." No treatment was given. In January 1947 she was admitted to that hospital with pneumonia, and received 1,400,000 units of penicillin (40,000 u. I.M. q. 3 h.). She showed anemia, jaundice, ascites and splenomegaly. The Kline and Mazzini tests were strongly positive.

On admission here the same general physical findings were noted, the lower molar teeth were of the "mulberry type," and the anterior-posterior diameter of the upper central incisors was increased. X-ray films of the long bones and skull revealed no abnormalities. Fluoroscopic and film studies of the chest show no abnormalities in heart, aorta or esophagus. The most significant admission laboratory findings are shown in table 1.

Therapy during her 47-day stay in this hospital consisted of the general measures indicated; and 10,830,000 units of sodium penicillin and 700 mg. of bismuth subsalicylate intramuscularly. Crude liver extract was given intramuscularly every other day. Operative intervention, in the opinion of a surgical consultant, was not justified. The patient's course in the hospital was uneventful. She was discharged unimproved. She was to continue weekly injections of bismuth subsalicylate and crude liver extract. A letter was received from her home physician stating that she died on December 11, 1947, following a severe gastrointestinal hemorrhage. Autopsy was not permitted.

Table 1.—*Abstract of relevant laboratory data on admission* [1]

Test	Case No. 1	Case No. 2
Red cell count	3,480,000	3,500,000.
White cell count	3,000	2,500.
Hemoglobin	7.5 gm.	8.5 gm.
Platelet count	126,000	155,000.
Differential	Normal	Normal.
Sternal marrow		Normal.
Fragility	Initial: 0.36 percent; Complete: 0.28 percent	
Wassermann	Strongly positive	Strongly positive.
Kahn	Strongly positive	Strongly positive.
Kahn titer	16 units	16 units.
Spinal fluid	Normal	Normal.
Bromosulphalein	15 percent retained	28 percent retained.
Prothrombin time	23 seconds	20 seconds.
	Control 12 seconds	Control 15 seconds.
Icterus index	60	9.
Van den Bergh	Strongly positive direct; 3.6 mg./100 cc. indirect;	
Total protein	6.7 gm. percent	4.7 gm. percent.
A/G ratio	1/1.7	1/1.6.
Hippuric acid excretion	0.3 gm. in 1 hour	0.5 gm. in 1 hour.
Cephalin flocculation	Three-plus	Four-plus.
Cholesterol	136 mg./100 cc.	
Urine albumin	One-plus	Negative.
Urine bilirubin	Two-plus	Negative.
Urine urobilin	Two-plus	Negative.

[1] There were no significant changes later.

Case 2.—W.P.M., white male, age 24, was admitted to the University of Virginia Hospital (#237254) on March 3, 1947. His chief complaint was recurrent, painless swelling of the abdomen for 2 years. There had been no jaundice. The patient had been diagnosed as having syphilis in May 1943, and had received a course of bismuth injections at that time.

The patient was an asthenic man with a chronically ill appearance. The heart size was normal; there were harsh systolic murmurs over the apical and pulmonic areas. Marked protuberance of the abdomen was noted with a fluid wave elicited. The liver was not palpable, but the spleen, smooth and firm in consistency, was felt at the level of the umbilicus. A chest plate revealed the diaphragm to be markedly elevated, the lung fields being clear. Fluoroscopic studies of the esophagus were normal. Some of the admission laboratory findings are summarized in table 1.

Supportive therapy, 5,913,000 units of sodium penicillin intramuscularly, 67 mg. of clorarsen intravenously, and liver concentrate ("Intraheptol") intravenously were given. A surgical consultant felt that operative intervention was not indicated. During the last month of his hospital stay his general condition improved symptomatically.

He was readmitted to the hospital in May 1947 and July 1947 with little change noted in his clinical picture and laboratory studies. Therapy consisted of general management, 14,050,000 units of sodium penicillin, 90 mg. of clorarsen and liver concentrate. His course in the hospital was uneventful, and he was discharged unimproved on August 7, 1947. A letter from the patient's mother stated that the patient had died on December 14, 1947. The cause of death was not clear as the letter stated that "he had burst."

Comment

These two cases, when first seen, presented the picture of the late stage of Banti's syndrome. There was marked evidence of severe liver disease, anemia, and leukopenia. Thrombocytopenia was not striking.

Although diagnosed as syphilitic 20 months and 48 months, respectively, prior to admission, neither had received adequate antisyphilitic therapy.

Many surgical procedures have been tried in an effort either to relieve the portal hypertension or to cope with the gastrointestinal hemorrhage. The results with splenectomy were not uniform. Recently, various shunts of the portal circulation using the splenic and renal veins or the portal vein and the inferior vena cava have been attempted.

The effects of antisyphilitic therapy in cases of diffuse hepatic disease associated with syphilis have been poor. In contrast, in cases where a gummatous lesion predominates results have been striking. Stokes (*15*) cautions against the use of arsenicals in hepatic syphilis because of their potential toxicity. However, arsenicals used cautiously have been of therapeutic value.

It was hoped with the introduction of penicillin, a nontoxic

agent, that the treatment of late splenohepatic syphilis would be enhanced. Struble and Bellows (*16*), studying the distribution of penicillin in tissues of dogs, found 4.77 units per gram of liver tissue 1 hour after a single intravenous injection of 12,800 units per kilogram. Tucker and Dexter (*17*) reported two cases of gummatous involvement of the liver which responded dramatically to penicillin.

Total dosages of 12,230,000 units and 19,963,000 units respectively were given to the two cases herein reported. The first case received 700 mg. of bismuth subsalicylate; the second case 157 mg. of clorarsen. There was no evidence either by symptoms and signs or by laboratory studies that a Herxheimer reaction or therapeutic paradox occurred. No improvement was noted in the condition of either patient. Repeated studies of liver function showed no increase in hepatic function.

Conclusions

1. There is a large amount of evidence to support the concept that Banti's syndrome is due to mechanical obstruction in the portal system.

2. Late syphilis of the liver, productive of an intrahepatic portal obstruction, may result in Banti's syndrome.

3. Penicillin in large total dosages failed to alter the course of advanced Banti's syndrome associated with syphilis.

4. It is probable that no form of antisyphilitic therapy will improve the prognosis in these late cases.

References

1. Banti, G.: Splenomegaly with cirrhosis of the liver. Med. Classics, 1: 913, 1937.
2. Rives, J. D.: The splenic anemias. South. Surgeon, 9: 328, 1940.
3. McMichael, J.: Pathology of hepatolienal fibrosis. J. Path. & Bact., 39: 481, 1934.
4. Rousselot, L. M.: Congestive splenomegaly. Bull. New York Acad. Med., 15: 188, 1939.
5. Thompson, W. P.: Pathogenesis of Banti's disease. Ann. Int. Med., 14: 255, 1940.
6. Johnston, J. M.: The relation of changes in the portal circulation to splenomegaly of the Banti's type. Ann. Int. Med. 4: 772, 1931.
7. Thompson, W. P.; Coughey, J. L.; Whipple, A. O.; Rousselot, L. M.: Splenic vein pressure in congestive splenomegaly. J. Clin. Investigation, 16: 571, 1937.
8. Herrick, F. C.: An experimental study into the cause of the increased portal pressure in portal cirrhosis. J. Exper. Med., 9: 93, 1907.
9. Rousselot, L. M.; Thompson, W. P.: Experimental production of congestive splenomegaly. Proc. Soc. Exper. Biol. & Med., 40: 705, 1939.
10. Whipple, A. O.: The problem of portal hypertension in relation to the hepatosplenopathies. Ann. Surg., 122: 449, 1945.
11. Turner, H. J.: Cirrhosis of liver. In H. L. Bockus: Gastroenterology. 2nd Ed. W. B. Saunders & Co., Philadelphia, 1946. Vol. III, p. 314.

12. Councilman, W. T.: Case report. Johns Hopkins Hosp. Med. Bull., 2: 18, 1891.
13. Osler, W.: On splenic anemia. Am. J. M. Sc., 119: 54, 1900.
14. Korns, H. M.: Tertiary syphilis of the liver simulating banti's syndrome. Am. J. M. Sc., 179: 811, 1930.
15. Stokes, J. H.; Beerman, H.; Ingraham, N. A.: Modern Clinical Syphilology. 3rd Ed., W. B. Saunders Co., Philadelphia. Pp. 846–892, 1945.
16. Struble, G. G.; Bellows, J. G.: Studies on the distribution of penicillin in the eye and its clinical application. J.A.M.A., 125: 685, 1944.
17. Tucker, H. A.; Dexter, D. D.: Penicillin treatment of gummatous hepatic syphilis. Report of 2 cases. Arch. Int. Med., 78: 313, 1946.

Treatment of Gonorrhea with Oral Penicillin[1]

Adolph Jacoby and Arthur H. Ollswang

A study to determine the value of treatment of gonorrhea by penicillin administered orally is herewith reported.

Patients in this study were of both sexes, having the disease in varying stages but predominantly with acute infections. The diagnosis was made by the detection of gonococci in the smears and cultures of the discharges present. Cure was determined when symptoms had disappeared and three successive smears and cultures taken at weekly intervals from the urethra and prostate in the male and urethra and cervix in the female were negative.

The medication used was tablets of crystalline penicillin G buffered with glycerides and sodium salts of fatty acids or with aluminum hydroxide.[2] The dosages employed ranged from 100,000 units to 600,000 units. In many of the patients the medication was administered as a single dose taken by the patient while in the clinic. The first dose employed was 100,000 units which was administered to 12 males and 1 female patient. All of these patients failed to respond. The dose was then increased to 200,000 units. This dose was given to 2 males and 1 female. All of them failed to respond. The dose was doubled, 400,000 units being used. This group which has already been reported in previous communications (*1*) received 100,000 units every 4 hours for 4 doses. There were 178 males and 18 females so treated. Of the 178 males, 146 or 82 percent were cured. Of the 18 females, 13 or 72.2 percent were cured. The dose was then increased to 500,000 units given at one time. There were 17 males and 3 fe-

[1] From the Bureau of Social Hygiene, Department of Health, City of New York. Read by title at the meeting of the Syphilis Study Section and the American Venereal Disease Association on April 7–8, 1949, at Washington, D. C.

[2] Oral penicillin tablets supplied by Commercial Solvents Corp.

males. Of the 17 males, 14 or 82.4 percent were cured. All of the females were cured. The dose was then increased to 600,000 units taken in one dose. Seventy-seven patients, 75 males and 2 females, were so treated. Of these, 63 males or 84 percent and 2 females or 100 percent were cured.

Table 1.—*Oral penicillin—results of treatment*

Oral penicillin dose	Total		Cured				Failed			
	Male	Female	Male	Percent	Female	Percent	Male	Percent	Female	Percent
Units										
100,000	12	1					12	100.0	1	100
200,000	2	1					2	100.0	1	100
400,000 (1)	178	18	146	82.0	13	72.2				
500,000	17	3	14	82.4	3	100.0	3	17.6		
600,000	75	2	63	84.0	2	100.0	12	16.0		

The blood levels were obtained by the Rammelkamp dilution method, using *Streptococcus hemolyticus* group A as the test organism. These results are indicated in the accompanying table.

Table 2.—*Penicillin blood levels* [1]
(Units per cubic centimeter)

Dosage of oral penicillin	1 hour	2 hours	3 hours	4 hours	6 hours	9 hours	12 hours	18 hours	24 hours
Units									
100,000			0.01		0.01	0.01			
200,000			.01–.04				0.01		
400,000			.08						
500,000			.04–.16		.02	.01	.01		0.01
600,000	.08–.16	.01	.02–.08	.01–.08	.005–.08		.005–.01		
1,000,000			.16–.32					.01	

[1] Performed by Miss Carolyn R. Falk, Bureau of Laboratories, Department of Health, City of New York.

From these statistics it would seem that the percentage of cures obtained with dosages ranging from 400,000 to 600,000 units is practically identical. Although this group is not large enough for a very accurate statement of therapeutic efficiency, yet the percentages of cure recorded would seem to indicate that oral therapy, especially when administered in a single dose in the physician's presence will prove to be a practical, painless, and satisfactory therapeutic procedure.

Reference

1. Jacoby, A.; Ollswang, A. H.; Freund, J.; Rosenthal, T.: Ambulatory treatment of gonorrhea with penicillin preparations. Am. J. Syph., Gonor. & Ven. Dis., 32: 133, 1948.

Urethral Stricture—Sequela of Gonorrhea

R. Frank Jones [1]

(These observations will be reported in detail at a later date.)

[1] From the Department of Surgery, Howard University.

The Use of Cardiolipin-Lecithin in the Preparation of Indicator (Antigen) for Hinton Test

William A. Hinton,[1] Genevieve O. Stuart,[2] and James F. Grant [3]

Soon after the Wassermann test was devised in 1906, research was begun to develop better serologic technics for syphilis. It is still continuing although the best of the tests are quite good in the detection of syphilis, and are highly specific except for certain diseases which, in varying percentages, may give a positive reaction in nonsyphilitic persons. Those who have made a critical study of syphilis based on actual clinical observations, and not on immunologic or serologic *theories* have recognized that there still remains great room for improvement in the sensitivity of these tests. This paper is being presented largely to show how much one of the United States "approved" serologic tests for syphilis can be improved in sensitivity without rendering it unsatisfactory because of positive reactions in nonsyphilitic persons almost free from diseases which may cause false positive reactions.

This improvement was accomplished with the Hinton test by using for indicator [4] (antigen) alcoholic solutions of cardiolipin and lecithin prepared by Pangborn (*1*) and subsequently fortified with cholesterol. For the group of cases upon which this paper is based each cubic centimeter of the stock indicator contained 1.2 mg. of cardiolipin, 7.61 mg. of lecithin, and 2.4 mg. of cholesterol. One cubic centimeter of this particular mixture was the equivalent by volume to 1 cc. of the standard stock Hinton indicator and was

[1] Physician-in-chief, Department of Clinical Laboratories, Boston Dispensary, and Chief of the Wassermann Laboratory, Massachusetts Department of Public Health.

[2] Assistant Bacteriologist, Wassermann Laboratory, Massachusetts Department of Public Health.

[3] Supervising Technician, Department of Clinical Laboratories, Boston Dispensary.

[4] In this paper the word "indicator" will be used instead of antigen, an incorrect term, whenever employed in connection with serologic tests for syphilis. This use of the word should have been discarded over 40 years ago.

the amount necessary for the preparation of 30 cc. of the mixed indicator. Although the sensitivity of this mixed indicator was maximal, others of the same sensitivity were prepared from different lots of ingredients obtained from Pangborn, and one from Lederle.[5]

The technic of the test, except for the substitution of cardiolipin-lecithin for the alcoholic extract of beef heart (Difco) in the preparation of stock indicator, is that described in the "Technics of Serodiagnostic Tests for Syphilis, 1944" (*2*). Moreover, the tests with cardiolipin-lecithin indicator are easier to read and the reactions on the whole much stronger.

Group I (S.B.B.) in table 1 afforded material by which it was possible to measure the specificity of the Hinton test when cardiolipin-lecithin indicator was used. These persons had offered themselves as donors in connection with the Massachusetts State Blood Bank. In this State they may be presumed to be nonsyphilitic with a very few exceptions: First, because they come from a group in which the incidence of positive reactions has been found to be very low with the standard Hinton test, which is quite generally regarded as one of the most sensitive of the "approved" tests that are used for diagnostic purposes. Indeed, in the early evaluations conducted under the joint auspices of the American Society of Clinical Pathologists and the United States Public Health Service, its sensitivity was so high that it was regarded by some as unsatisfactory for diagnostic purposes. These authorities believed that because of the high sensitivity of the standard Hinton test, false positives would be obtained to an objectionable degree. That this assumption was erroneous can be judged by the fact that Vonderlehr's table (*3*) of the prevalence of syphilis based on blood tests among the first million selectees and volunteers for World War II shows that four of the New England States had less than 0.8 percent of positive reactions based on the Hinton test—Massachusetts had 0.55 percent and except for Wisconsin, this was the lowest of any of the 45 States listed and the District of Columbia. The number of persons tested in each of these States was sufficient to judge reliably the maximum incidence of false positive reactions, for assuming that none of the positive reactions obtained with the Hinton test by these States was due to syphilis, the percent of

[5] As yet an indicator of this potency is not available commercially. It is hoped that it will be in the near future and until then it is not deemed advisable to attempt to perform the test using the proportions of cardiolipin and lecithin stated above because the attainment of the levels of specificity and sensitivity obtained by us can only be determined by trying varying proportions of these ingredients in the actual testing of a large number of syphilitic and nonsyphilitic persons and choosing the preparations which are found to be optimal; and the preparation of both cardiolipin and lecithin is far too complicated for the average serologic laboratory to undertake if trustworthy products are to be expected.

specificity would be 99.2 percent which is greater than that required by the American Serologic Advisory Committee.

The little variation in the incidence of positive reactors in these New England States (from 0.55 percent to 0.78 percent) gives excellent evidence of approximately uniform technical execution of the Hinton test by them, and thereby further strengthens the dependability of the tabulated results for statistical purposes. Of course, all of the positive reactors obtained in this group of New England States cannot be regarded as false positives because syphilis is known to exist in New England!—even though the percentage is quite low as compared with most of the other States. Indeed, in Massachusetts, each of the selectees who had a positive reaction was investigated epidemiologically and about half of them were finally found to be syphilitic. This would give an incidence of true false positive reactions of between 0.2 percent and 0.3 percent. Translating this into terms of specificity, the percent for the Hinton test would be between 99.7 percent and 99.8 percent, a very high rate which is statistically reliable because it is based on 17,542 cases, representing people from all walks of life and most of them at the time of their blood examination were free from such diseases as would be likely to cause a false positive reaction.

With the use of cardiolipin-lecithin indicator the percent of negative reactors in group I (S.B.B.) in table 1 was 99.78 percent, and if we assume that all of the 0.22 percent of positives were false positive reactions, which is unbelievable, the fact is unescapable that the specificity of the Hinton test with cardiolipin is very high.

The sensitivity of serologic tests for syphilis has been a matter of major concern to us for many years for I believe that a test which is inferior in the detection of the disease poorly performs its chief function. The senior author remembers that soon after the first American national evaluations some authorities defended the use of a test whose sensitivity was below 60 percent when other technics gave within a few tenths of 90 percent. Of course such a defense was untenable.

The great difficulty in reliably establishing a sensitivity level for serologic tests for syphilis grows out of the fact that the evaluations are necessarily limited to the testing of relatively few presumably nonsyphilitic persons in order to find the specificity percent. This puts the truly sensitive test on the spot, because the obtaining of even two positives in one hundred presumably nonsyphilitic persons renders the specificity of a test unsatisfactory. This places an unwarranted reliance on serologic tests in the determination of the nonsyphilitic status of the evaluated material, for truly syphilitic persons often give no history or clin-

ical evidence of syphilis. I may illustrate as follows: Suppose four different technics give a negative reaction with a given specimen from a presumably nonsyphilitic person, and the fifth technic gives a positive result, the conclusion may be drawn that the individual involved is nonsyphilitic, a presumption which is often totally wrong as any serologist knows if he simultaneously has done five different tests routinely on each specimen of blood obtained from a clinic in which the patients are all known to be syphilitic as determined by history and past or present clinical evidence of the disease. Therefore, the evaluation of a large number of laboratories based on the testing of relatively few presumed nonsyphilitic persons tends to frighten an author-serologist from attempting to step up greatly the sensitivity of his test.

In this study, with an adequate number of negative controls, (6,325 persons), we are able to place even greater reliance on the results obtained in group II (Skin Clinic). These patients were from a clinic whose clientele is largely syphilitic. Here in a total of 854 cases, the cardiolipin-lecithin indicator gave positive reactions in 405 known syphilitics as compared with 273 with the standard indicator. This is a ratio of 148 : 100. In other words, the capacity to detect the disease with the cardiolipin-lecithin indicator is about 1½ times that obtained with the standard indicator.

Table 1 contains other groups of cases which are included largely to indicate the relative incidence of positive reactions obtained with the cardiolipin-lecithin and standard indicators. In all of these institutions specimens are taken routinely on each admission and there were very few instances in which the tests were repeated. These were confined almost solely to those who gave a positive reaction with the cardiolipin-lecithin indicator and a negative or doubtful reaction with the standard indicator.

Groups III and IV were patients being treated in the Department of Genito-urinary Diseases and the Department of Gynecology of a Boston Medical Center. Most of these patients currently had gonorrhea which establishes their exposure to venereal disease. The percent of negative reactors in the two groups was essentially the same, leaving from 3 percent to 3.5 percent who possibly had syphilis. This percent is not high for persons most of whom had been exposed to venereal disease.

Group V consists of persons who were admitted to the Medical Department of the above Medical Center with a history that did not suggest signs or symptoms of active venereal disease. The size of the group is statistically significant and the percent of negatives (98.33 percent) is higher than I would expect from the stratum of society to which this clientele belongs.

Table 1.—*Results of Hinton test with standard and cardiolipin-lecithin (Paugborn) indicators*

Group	Institution	Indicators: Standard Hinton, cardiolipin-lecithin	Results												Number of patients
			Negative Negative		Positive Positive		Negative Positive		Doubtful Positive		Negative Doubtful		Doubtful Doubtful		Doubtful Negative		
			Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
I	S.B.B.		6310	99.76	7	0.11	2	0.03	3	0.05	2	0.03	0	0.0	1	0.02	6,325
II	B.D.—Skin department		436	51.05	273	31.96	76	8.9	56	6.55	13	1.5	0	.0	0	.0	854
III	B.D.—Genito-urinary department		257	96.98	3	1.13	4	1.51	1	.38	0	.0	0	.0	0	.0	265
IV	B.D.—Gynecology department		86	96.63	2	2.23	1	1.1	0	.0	0	.0	0	.0	0	.0	89
V	B.D.—Medical department		590	98.33	2	.33	5	.83	3	.5	0	.0	0	.0	0	.0	600
VI	P.D.H.		2164	98.95	8	.37	13	.59	1	.05	1	.05	0	.0	0	.0	2,187
VII	L.C.		4433	97.45	77	1.69	19	.42	17	.37	2	.04	1	.02	0	.0	4,549
VIII	F.H.		414	97.18	2	.47	6	1.4	1	.23	3	.7	0	.0	0	.0	426
IX	B.I.I.		689	98.0	9	1.28	3	.43	1	.14	1	.14	0	.0	0	.0	703
X	L.S.		34	94.44	1	2.77	0	.0	1	2.77	0	.0	0	.0	0	.0	36
XI	P.H.		146	85.38	16	9.36	4	2.34	4	2.34	1	.58	0	.0	0	.0	171
																	16,205

Group VI (P.D.H.) is a diagnostic hospital. Most of the patients were persons who were diagnostically puzzling, which is particularly true of many cases of syphilis. Consequently, it is our impression that, despite the relatively high social status of these patients only 98.94 percent gave a negative reaction.

Group VII (L.C.) is from another institution the patients of which are apt to present diagnostic problems, and the patients for the most part belong to well-to-do classes. There were 97.4 percent of negatives. This is in close agreement with group VI as was expected.

Group VIII (F.H.), on the other hand, is a relatively small hospital, the clientele of which consists of the middle and upper classes. However, being a general hospital for acute diseases requiring hospitalization, it might be expected that the percent of negative reactors would be somewhat lower than that of groups VI and VII.

Group IX (B.L.I.) is a maternity hospital and the number of cases is statistically significant. It is my impression that possibly 0.5 percent of these patients gave a false positive test.

Group X (L.S.) is from a hospital for tuberculosis. The number is too small to have statistical significance.

Group XI (P.H.) consists of patients in the hospital solely for cancer, and here the percent of negative reactors is 84.9 percent. This would lead to the belief that false positives are not uncommonly found among cancerous patients with the cardiolipin-lecithin indicator. In an unpublished statistical study, made some years ago, it was found that patients with cancer of the mouth, tongue, tonsils, and liver had positive Wassermann reactions considerably in excess of the percent found in other cancerous patients of the same social and economic status.

Comment

It is generally recognized that a serologic test for syphilis that possesses high specificity and the maximum of sensitivity is a desirable aid in the management of syphilis. These are among the chief advantages: (1) generally speaking, the more sensitive the test, the earlier is syphilis detectable; (2) the more sensitive test is of especial advantage to both the physician and the patient in the management of syphilis, particularly of less than 4 years' duration because even though the patient may not require treatment during the entire period of his positivity the increased duration of positivity generally secures better co-operation of the patient in lengthening the period of his observation; (3) a test of

maximum sensitivity and high specificity is of great importance in the differential diagnosis of conditions which may be either syphilitic or caused by another disease.

Conclusion

Both extremely high sensitivity and specificity were obtained by employing cardiolipin-lecithin (Pangborn) indicator in the Hinton test.

References

1. PANGBORN, M. C.: Proc. Soc. Exper. Biol. & Med., 48: 484, 1941.
2. Technics of Serodiagnostic Tests for Syphilis, 1944. Venereal Disease Education Institute, Raleigh, N. C. (Revised ed.: Manual of Serologic Tests for Syphilis, 1949. Superintendent of Documents, Government Printing Office, Washington 25, D. C.)
3. VONDERLEHR, R. A.; USILTON, L. J.: J. Am. Med. Assoc., 117: 1350, 1351, October 18, 1941.

False Positive Serologic Tests for Syphilis Due to Newcastle Virus Infection

Abraham Gelperin, The School of Medicine, Yale University

(These observations will be reported in detail at a later date.)

☆ U. S. GOVERNMENT PRINTING OFFICE: 1949—838210